The Impact of Erythropoietin on Short- and Long-Term Kidney-Related Outcomes in Neonates of Extremely Low Gestational Age. Results of a Multicenter, Double-Blind, Placebo-Controlled Randomized Clinical Trial

David J. Askenazi, MD, MSPH[1], Patrick J. Heagerty, PhD[2], Robert H. Schmicker, MS[2], Patrick Brophy, MD[3], Sandra E. Juul, MD, PhD[4], Stuart L. Goldstein, MD[5], Sangeeta Hingorani, MD, MPH[4], on behalf of the PENUT Trial Consortium*

Objective To evaluate whether extremely low gestational age neonates (ELGANs) randomized to erythropoietin have better or worse kidney-related outcomes during hospitalization and at 22-26 months of corrected gestational age (cGA) compared with those randomized to placebo.

Study design We performed an ancillary study to a multicenter double-blind, placebo-controlled randomized clinical trial of erythropoietin in ELGANs.

Results The prevalence of severe (stage 2 or 3) acute kidney injury (AKI) was 18.2%. We did not find a statistically significant difference between those randomized to erythropoietin vs placebo for in-hospital primary (severe AKI) or secondary outcomes (any AKI and serum creatinine/cystatin C values at days 0, 7, 9, and 14). At 22-26 months of cGA, 16% of the cohort had an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2, 35.8% had urine albumin/creatinine ratio >30 mg/g, 23% had a systolic blood pressure (SBP) >95th percentile for age, and 40% had a diastolic blood pressure (DBP) >95th percentile for age. SBP >90th percentile occurred less often among recipients of erythropoietin ($P < .04$). This association remained even after controlling for gestational age, site, and sibship (aOR 0.6; 95% CI 0.39-0.92). We did not find statistically significant differences between treatment groups in eGFR, albumin/creatinine ratio, rates of SBP >95th percentile, or DBP >90th or >95th percentiles at the 2 year follow-up visit.

Conclusions ELGANs have high rates of in-hospital AKI and kidney-related problems at 22-26 months of cGA. Recombinant erythropoietin may protect ELGANs against long-term elevated SBP but does not appear to protect from AKI, low eGFR, albuminuria, or elevated DBP at 22-26 months of cGA. *(J Pediatr 2021;232:65-72)*.

Extremely low gestational age neonates (ELGANs; born <28 weeks of gestation) who graduate from the neonatal intensive care unit (NICU) often have organ dysfunction due to organ underdevelopment and/or organ damage during their initial hospitalization. David Barker is credited with the observation in 1997, that many "adult" diseases have their origins in fetal life.[1,2] Evidence for this "fetal programming" exists for infants born premature who go on to develop obesity,[3] hypertension,[2] insulin resistance,[4] coronary artery disease,[5] and chronic kidney disease (CKD)[6] later in life. A meta-analysis by White et al showed that infants of low birth weight (<2500 g) have an ~80% increased odds of albuminuria, 80% increased odds of a sustained low glomerular filtration rate, and an approximately 60% increased odds of dialysis-dependent CKD in later life compared than their counterparts born at term.[7] The incidence of CKD in ELGANs may be greater than what is reported in the meta-analysis by White et al, as the number of nephrons is lower in more neonates born premature. Acute kidney injury (AKI) is common in neonates of extremely low gestational age. We recently reported the AKI prevalence rates in a cohort of 923 ELGANs enrolled in a randomized trial of recombinant erythropoietin (rhEpo), entitled the Preterm Epo Neuroprotection Trial (PENUT),[8] in which 351 of 923 (38.0%) had at least 1 episode of stage 1 or greater AKI, and 168 of 923 (18.2%) had at least 1 episode of severe AKI anytime during the hospitalization.[8]

ACR	Albumin/creatinine ratio	GEE	Generalized estimating equations
AKI	Acute kidney injury	NICU	Neonatal intensive care unit
BP	Blood pressure	PENUT	Preterm Epo Neuroprotection Trial
cGA	Corrected gestational age	rhEpo	Recombinant human erythropoietin
CKD	Chronic kidney disease		
DBP	Diastolic blood pressure	SBP	Systolic blood pressure
eGFR	Estimated glomerular filtration rate	SCr	Serum creatinine
ELGAN	Extremely low gestational age neonate		

From the [1]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; [2]University of Washington, Seattle, WA; [3]University of Rochester/Golisano Children's Hospital, Rochester, NY; [4]Department of Pediatrics, University of Washington/Seattle Children's Hospital, Seattle, WA; and [5]Department of Pediatrics, Cincinnati Children's Hospital Medical Center/University of Cincinnati College of Medicine, Cincinnati, OH

*List of additional members of the PENUT Trial Consortium is available at www.jpeds.com (**Appendix**).

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Erythropoietin is best known for its hematopoietic effects; however, it also has tissue-protective effects in clinical models and human studies across several organ systems.[9] Erythropoietin receptors are present on glomerular, mesangial, and tubular epithelial kidney cells.[10] Animal studies of ischemia–reperfusion injury and sepsis-induced AKI show that rhEpo preserves kidney function, protects renal proximal tubular cells by decreasing apoptosis, and decreases proinflammatory cytokine expression in the renal cortex.[11-15] These effects are independent of changes in renal hemodynamics.[13] Song et al demonstrated a reduction in AKI in a small clinical trial of 71 adults who underwent elective coronary artery bypass graft surgery and were randomized to rhEpo (300 units/kg intravenous × 1) vs placebo.[16] Long-term outcomes from this cohort reported by Oh et al showed a reduction in all-cause mortality ($P < .03$) and a reduction in the composite of all-cause mortality and kidney failure ($P < .01$) in those randomized to rhEpo.[17] In contrast, a randomized clinical study of 606 adults with traumatic brain injury randomized to 40 000 units rhEpo IV vs placebo found no renoprotective effect of rhEpo.[18]

To determine whether rhEpo improves the short- and long-term kidney outcomes in ELGANs, we performed an ancillary study of PENUT, a multicenter randomized clinical trial that randomized ELGANs to receive high-dose rhEpo or placebo. Our primary hypothesis was that ELGANs randomized to rhEpo would have a lower rate of in-hospital severe AKI and lower rates of CKD, albuminuria, and elevated blood pressure at 22-26 months of corrected gestational age (cGA).

Methods

The PENUT trial is a randomized, placebo-controlled, double-blind clinical trial of rhEpo in ELGANs performed across 19 academic centers and comprised of 30 NICUs across 13 states in the US from December 2013 to September 2016. PENUT screened 3366 neonates, of whom 941 were enrolled in the study. The reasons for nonenrollment have been described in detail elsewhere.[19,20] The inclusion criteria included (1) inborn patients born between $24^{0/7}$ and $27^{6/7}$ weeks of gestation in participating NICUs, (2) less than 24 hours of age, (3) parental informed consent obtained, and (4) available arterial or venous access. Exclusion criteria included (1) major life-threatening anomalies (brain, cardiac, and chromosomal anomalies); (2) hematologic crises such as disseminated intravascular coagulation or hemolysis due to blood group incompatibility; (3) hematocrit >65%; (4) hydrops fetalis; and (5) known congenital infection.

Of the 941 subjects enrolled in the study, we excluded 18 neonates (4 who died before receiving study drug, 1 who was enrolled incorrectly, and 13 who died on days 0, 1, or 2) because we were unable to ascertain whether these neonates had AKI, given that it takes days for serum creatinine (SCr) to rise after an event and maternal SCr values affect neonatal SCr in the first postnatal days.[21,22] Therefore, the final sample of ELGANs for the short-term outcomes includes the 923 subjects who received rhEpo (N = 469) or placebo (N = 454) and were alive on day 3 (**Figure 1**; available at www.jpeds.com).

For the 22-26 months' cGA time point, 383 of 420 (91.2%) participants who were alive at 2 years and received rhEpo returned for follow-up (49 died before the follow-up time point, 35 were lost to follow-up, and 2 were missing 24-month data). Urine, blood, and blood pressure measurements were not a mandatory part of the primary protocol but were encouraged by site personnel to families. **Figure 1** shows the breakdown of data ascertainment. Of the 383 subjects who received rhEPO and returned for a follow-up visit, 123 of 383 (32.1%) had both blood and urine collected, 47 of 383 (12.7%) had blood only, 104 of 383 (27.2%) had urine only, and 109 of 383 (28.5%) had neither blood nor urine collected for analysis. Of the 383 subjects who returned for follow-up, 233 of 383 (60.8%) had blood pressure measured and 150 of 383 (39.2%) did not.

Alternatively, 397 of 412 (96.4%) participants who received placebo returned for follow-up (42 died before 24 months, 13 were lost to follow-up, 2 were missing a 24-month status). Of the 397 who came to follow-up visit, 140 of 397 (35.3%) had both blood and urine collected, 50 of 397 (12.6%) had blood only, 78 of 397 (19.6%) had urine only, and 129 of 397 (32.5%) had neither blood nor urine collected. Of the 397 subjects who came for a follow-up visit, 258 of 397 (65.0%) had blood pressure measured and 139 of 397 (35.0%) did not.

The University of Washington institutional review board approved this collaborative study, and each center received approval from their respective institutional review boards.

Timeline of Clinical Trial

The design and primary efficacy/safety outcomes have been published elsewhere.[19,20] In brief, after informed consent, participants were randomized to rhEpo vs placebo within 24 hours of birth. Randomization allocation was 1:1, with patients stratified by gestational age category, multiple births, and study site. Sample size was determined by the primary study to be able to detect a difference in the primary outcome (death or neurologic disability at 22-26 months of cGA). Subjects received rhEpo at a dose of 1000 units/kg or placebo intravenously every 48 hours for a total of 6 doses; thereafter, participants received either 400 U/kg/dose rhEpo subcutaneously or sham injections 3 times a week until they reached $32^{6/7}$ weeks of cGA. Study personnel and families were still blinded to randomization groups at the follow-up visit.

AKI Definitions and Time Frames of Assessments for AKI Using Clinical SCr Data

We used the SCr-based Kidney Disease Improving Global Outcomes criteria to define neonatal AKI using clinically

measured SCr values.[23] Each NICU measured SCr according to their institutional guidelines using the local laboratory methodology available (11 Jaffe, 8 enzymatic). Our a priori primary short-term outcome was severe AKI any time during the hospitalization. Severe AKI is defined as reaching stage 2 or greater AKI as previously described in other multicenter neonatal[24] and pediatric[25] AKI studies whereby the neonates had to have a ≥200% SCr rise from baseline anytime during the NICU hospitalization. The baseline SCr is defined as the lowest previous value measured (not including any values measured on the day of birth or on the day after birth). The earliest baseline SCr value used to define AKI in this study is on postnatal day 2, as day of birth is denoted as day 0. We chose to exclude the SCr measured on the day of birth or the day after birth because these values represent maternal SCr, which plateaus over the next 36-48 hours in ELGANs.[22] Thus, in our study, it is not until day 3 when a rise in SCr from baseline can be detected. The 23 of 923 (2.5%) neonates who did not have any SCr values were classified as having no AKI.

For the secondary short-term outcomes, we evaluated AKI stages at different time points as follows: AKI was classified into early (days 3-7), middle (days 8-14), and late (days 15-discharge or 44 weeks of cGA, whichever comes first) as we have previously reported.[8] For these analyses, we included those patients who were alive at the beginning of each time frame such that we report on 923 infants during the first week, 891 in the middle time frame (due to 32 deaths between days 3-7), and 875 in the late time frame (due to 48 deaths between days 3-14). We define any AKI as the greatest AKI stage during the entire hospital stay.

Assessment of Short-Term Kidney Function Using SCr and Serum Cystatin C at Specific Predetermined Time Points

Using convenience blood samples drawn at time points determined by the primary study (postnatal days 0, 7, 9, and 14), we analyzed SCr (measured at a core laboratory in Seattle, Washington) using the 2-point method with the Vitros 4600 (Ortho Clinical Diagnostic). Cystatin C concentrations were analyzed using the same blood samples at the same core laboratory using particle-enhanced immunonephelometry with the BN ProSpec System (Simiens Helathineers). These analyses allow us to evaluate kidney function at standardized time points, with samples measured using the same methodology on the same postnatal days for the majority of infants. We report both SCr and cystatin C values as absolute measures and changes in the values over time.

Kidney-Related Measurements at the 22- to 26-Month cGA Visit

We defined estimated glomerular filtration rate (eGFR) according to the SCr and cystatin CKiD equation where eGFR (mL/min per 1.73 m^2) = 41.6 [ht (cm)/Scr (mg/dL)]$^{0.443}$ * [1.8/cystatin C (mg/L)]$^{0.479}$.[26] Urine was collected as a bag specimen or with a cotton ball in the diaper. We defined albuminuria as an albumin/creatinine ratio (ACR) >30 mg albumin/g creatinine, which has been shown to be a surrogate outcome of CKD progression in children.[27] Although there are very few data on normative values of ACR in the US, a study from the Netherlands reports ACR in 1288 toddlers at around the age of 24 months (median = 14 mg/g; IQR of 8-25.6; 5th percentile = 4.3 and 95th percentile = 89.3). This study found that 23.4% of subjects had a urine ACR >30 mg/g.[28]

Blood pressure was measured with a Briggs Mabic Healthcare Manual Sphygmomanometer with blood pressure cuff appropriate for patient size, whereby the inflatable bladder width had to be at least 40% of the child's mid–upper arm circumference and the length between 80% and 100% of the mid–upper arm circumference. Standardization of procedures and personnel training was done across all sites. After the child was in a calm state, 2 manual blood pressure measurements at least 5 minutes apart were taken. The lowest systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. We report the lowest SBP and DBP of the two and describe the population's values and percentages that exceed the 90th and 95th percentiles for age and sex-related norms according to the 2017 Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[29] For purposes of analysis in the regression models, we focus only on the 90th percentile values.

Statistical Analyses

Baseline characteristics, AKI status, core SCr values, serum cystatin C values, and 2-year kidney-related outcomes were examined by treatment arm. The 2-year kidney-related outcomes were compared between groups using both the categorical outcomes (eGFR <90 mL/min/1.73 m^2, urine ACR >30 mg/g, SBP >90th percentile, SBP >95th percentile, DBP >90th percentile, and DBP >95th percentile) as well as the continuous values. Linear and logistic models were used to test for trends using generalized estimating equations (GEE) with clustering by sibship.[30] These models were used to determine the association between treatment arm and kidney-related binary outcomes (severe AKI, abnormal eGFR, albuminuria, SBP >90th percentile, and DBP >90th percentile). We performed a GEE model controlling for sibship whereby we evaluated the interaction term for each demographic × treatment arm to understand whether demographic variables were disproportionate in those who had blood pressure ascertained vs missing. We performed a sensitivity analysis to determine whether an alternative approach to reporting blood pressure (BP) (using the average, instead of the lowest BP) would have led to differences in treatment effect. Data management and analysis were conducted using R, version 5.3.1 (R Foundation for Statistical Computing).

Results

Short-Term Kidney Outcomes

Of the 923 neonates included in the short-term analysis, 51.9% were male, the average birth weight was 801 g, and

most (91.6%) received prenatal steroids. Maternal race was largely White (65%), Black (26%), and other (9%), and 21% self-identified as Hispanic. Demographic and delivery room intervention differences and maternal characteristics by treatment arm are shown in **Table I**. The treatment groups were well matched for demographic characteristics and protective perinatal therapies.

The prevalence rates for AKI in the entire cohort and by treatment arm are shown in **Table II**. For the entire cohort, 351 of 923 (38.0%, CI 34.8%-41.3%) had at least 1 episode of stage 1 or greater AKI, and 168 of 923 (18.2%, CI 15.7%-20.7%) had at least 1 episode of severe AKI anytime during the hospitalization. The rates of our primary outcome (severe AKI at any time) did not differ in those who received rhEpo vs placebo. No statistically significant differences were seen in the rates of early, middle, or late AKI between treatment groups. No statistically significant differences were seen in the trends of clinically measured mean SCr over time between groups over a 7-day and a 3-day window (**Figure 2**, A and B).

The SCr and the cystatin C values measured at the core laboratory on postnatal days 0, 7, 9, and 14 are reported by treatment arm in **Table III** (available at www.jpeds.com) and depicted in **Figure 3**, A and B (available at www.jpeds.com), respectively. There was no meaningful difference in either SCr or cystatin C values or changes over time by treatment group. Using the GEE models, we found no differences by treatment arm for early, middle, or late AKI and no differences for severe AKI (**Table IV**; available at www.jpeds.com).

Kidney-Related Outcomes at 22-26 Months of cGA

Table V shows the rates of kidney-related outcomes at 22-26 months of cGA by treatment arm. In participants who had eGFR available, 54 of 336 (16.2%) had an eGFR <90 mL/min/1.73 m^2. In participants who had urine available, 155 of 435 (35.6%) had a urine ACR >30 mg/g. Evaluation of 24-month cGA outcomes by treatment group shows that the rates of eGFR <90 mL/min/1.73 m^2 were 16.2% and 15.9% for the placebo and rhEpo groups, respectively (P = NS). The rates of urine ACR ratio >30 mg/g were 36.8% and 34.5% for the placebo and rhEpo groups, respectively (P = NS).

Of the participants who had blood pressure measured, 160 of 491 (32.6%) had a SBP >90th percentile, and 112 of 491 (22.8%) had a SBP above the 95th percentile for age. Evaluation of DBP showed that 262 of 491 (53.4%) had a DBP >90th percentile, and 199 of 491 (40.5%) had a DBP above the 95th percentile for age. Those randomized to rHepo were less likely to have SBP >90th percentile than those randomized to placebo (65/258 [27.9] vs 95/258 [36.8%]; P < .04). We did not find any differences in the rates of SBP >95th percentile or DBP >90th or 95th percentiles. Eight participants were on antihypertensive medications at 24 months (5 alodipine, 3 other). Of these 8 subjects, 5 were noted as having elevated SBP and DBP, 2 were normotensive, and 1 did not have a blood pressure measured at the 24-month follow-up visit.

Of the 191 participants who returned to follow-up and had blood, urine, and SBP and DBP measurements, 47 of 191 (24.6%) had no abnormalities, 67 of 191 (35.1%) had 1 abnormality, 54 of 191 (28.3%) had 2 abnormalities, 21 of 191 (11.0%) had 3 abnormalities, and 2 of 191 (1.0%) had all 4 abnormalities.

Table VI (available at www.jpeds.com) shows that of the patients who survived the NICU stay, there was a statistically significant difference in the "lost to follow-up" rate between those who were randomized to placebo vs rhEPO (13/412 [3.2%] vs 35/420 [8.3%]; P < .01). However, we did not find statistically significant differences in the rates of blood, urine, and blood pressure ascertainment by treatment arm for those who survived the NICU stay.

Table VII (available at www.jpeds.com) provides data on the demographics by treatment arm for survivors who had blood pressure ascertained vs missing to determine whether disproportionate differences in the rates of blood pressure ascertainment by treatment arm exist. Sex was the only demographic characteristic that reached a statistically significant level of P < .05, and prenatal steroids almost reached the level of statistical significance (P = .06).

Table VIII (available at www.jpeds.com) shows the GEE models for each of the kidney-related metrics expressed as continuous and categorical variables at 24 months of cGA. After we controlled for site, gestational age, and accounting for sibship clustering, participants who were randomized to rhEpo had lower odds of high SBP (aOR 0.60; 95% CI 0.39-0.92). We did not find statistically significant differences between treatment groups in low eGFR, ACR, or high DBP.

We performed a sensitivity analysis to determine whether our findings on the treatment effect of rhEpo and SBP would have changed if we chose to report BP as the average between 2 values, instead of the lowest of 2 blood pressure readings. Of those with at least 1 BP measurement in the placebo arm, 134 of 258 (60.1%) had 2 measurements. Of those with at least 1 BP measurement in the rhEpo arm, 155 of 233 (57.5%) had 2 measurements. **Table IX** (available at www.jpeds.com) compares these BP measures by treatment arm for the 2 approaches. Compared with the lowest BP approach, using the average BP approach increases the rate of SBP >90th percentile from 95 of 258 (36.8%) to 110 of 258 (42.6%) in the placebo arm and from 65 of 233 (27.8%) to 76 of 233 (32.6%) in the rhEpo arm. The GEE models for the independent odds of SBP >90th by treatment groups were almost identical (0.60 [0.39, 0,92] in the lowest BP approach vs 0.59 [0.39, 0,89] in the average BP approach).

Discussion

In this ancillary study of a multicenter double-blind, randomized clinical trial, we found that participants randomized

Table I. Demographic characteristics by treatment arm

Characteristics	Treatment arm			*P* value
	All	Placebo	Epo	
n	923	454	469	
Male, n (%)	479 (51.9%)	228 (50.2%)	251 (53.5%)	.35
Gestational age, wk, n (%)				.07
24	227 (24.6%)	117 (25.8%)	110 (23.5%)	
25	242 (26.2%)	122 (26.9%)	120 (25.6%)	
26	220 (23.8%)	117 (25.8%)	103 (22.0%)	
27	234 (25.4%)	98 (21.6%)	136 (29.0%)	
Birth weight, g, mean (SD)	801.1 (187.9)	793.2 (181.9)	808.8 (193.4)	.21
Birth length, cm, mean (SD)	32.9 (2.9)	32.8 (2.7)	33 (3.1)	.47
Size for gestational age				.55
Large, n (%)	104 (11.3%)	50 (11.0%)	54 (11.5%)	
Average, n (%)	739 (80.1%)	360 (79.3%)	379 (80.8%)	
Small, n (%)	80 (8.7%)	44 (9.7%)	36 (7.7%)	
Apgar 1 min, median (IQR)	4 (2, 6)	4 (2, 6)	4 (2, 6)	.14
Apgar 5 min, median (IQR)	7 (5, 8)	7 (5, 8)	7 (5, 8)	.74
Occipitofrontal circumference, cm, mean (SD)	23.1 (1.9)	23.1 (1.9)	23.1 (1.9)	.71
Number of fetuses, median (IQR)	1 (1, 2)	1.3 (0.5)	1.3 (0.6)	.67
Prenatal steroids, n (%)	831 (91.6%)	407 (91.5%)	424 (91.8%)	.84
1 dose	174 (20.9%)	76 (18.7%)	98 (23.1%)	.25
2 doses	575 (69.2%)	289 (71.0%)	286 (67.5%)	
3 doses	74 (8.9%)	39 (9.6%)	35 (8.3%)	
Delivery room resuscitation, n (%)				
Any	896 (97.1%)	446 (98.2%)	450 (95.9%)	.09
Oxygen	738 (80.0%)	365 (80.4%)	373 (79.5%)	.81
Positive pressure	797 (86.3%)	403 (88.8%)	394 (84.0%)	.04
Intubation	748 (81.0%)	374 (82.4%)	374 (79.7%)	.35
Surfactant	480 (52.0%)	240 (52.9%)	240 (51.2%)	.65
Chest compression	72 (7.8%)	37 (8.1%)	35 (7.5%)	.79
Resuscitation drugs	32 (3.5%)	14 (3.1%)	18 (3.8%)	.66

Table II. AKI status by treatment arm

AKI status	Treatment arm			*P* value
	All	Placebo	Epo	
n	923	454	469	
AKI max anytime, n (%)				.62
Stage 0	572 (62%)	274 (60.4%)	298 (63.5%)	
Stage 1	183 (19.8%)	105 (23.1%)	78 (16.6%)	
Stage 2	108 (11.7%)	47 (10.4%)	61 (13%)	
Stage 3	60 (6.5%)	28 (6.2%)	32 (6.8%)	
Severe AKI max anytime, n (%)				.20
Yes (stage 2 or 3)	168 (18.2%)	75 (16.5%)	93 (19.8%)	
No (stage 0 or 1)	755 (81.8%)	379 (83.5%)	376 (80.2%)	
AKI timing (max SCr)				
Early (days 3-7), n (%)				.76
Stage 0	811 (87.9%)	400 (88.1%)	411 (87.6%)	
Stage 1	92 (10%)	45 (9.9%)	47 (10%)	
Stage 2	11 (1.2%)	6 (1.3%)	5 (1.1%)	
Stage 3	9 (1%)	3 (0.7%)	6 (1.3%)	
Middle (days 8-14), n (%)				.91
Stage 0	749 (81.1%)	368 (81.1%)	381 (81.2%)	
Stage 1	90 (9.8%)	49 (10.8%)	41 (8.7%)	
Stage 2	41 (4.4%)	19 (4.2%)	22 (4.7%)	
Stage 3	11 (1.2%)	2 (0.4%)	9 (1.9%)	
Missing—due to deaths before day 8	32 (3.5%)	16 (3.5%)	16 (3.4%)	
Late (days 15 – discharge or 44 wk), n (%)				.56
Stage 0	626 (67.8%)	306 (67.4%)	320 (68.2%)	
Stage 1	117 (12.7%)	64 (14.1%)	53 (11.3%)	
Stage 2	84 (9.1%)	37 (8.1%)	47 (10%)	
Stage 3	48 (5.2%)	25 (5.5%)	23 (4.9%)	
Missing—due to deaths before day 15	48 (5.2%)	22 (4.8%)	26 (5.5%)	

Children who died on days 0, 1, or 2 are excluded from this analysis.
Laboratory data from days 0, 1 are not included in the AKI calculation.
Children may qualify as severe AKI on day 2 via elevated SCr but not by SCr ratio to baseline.

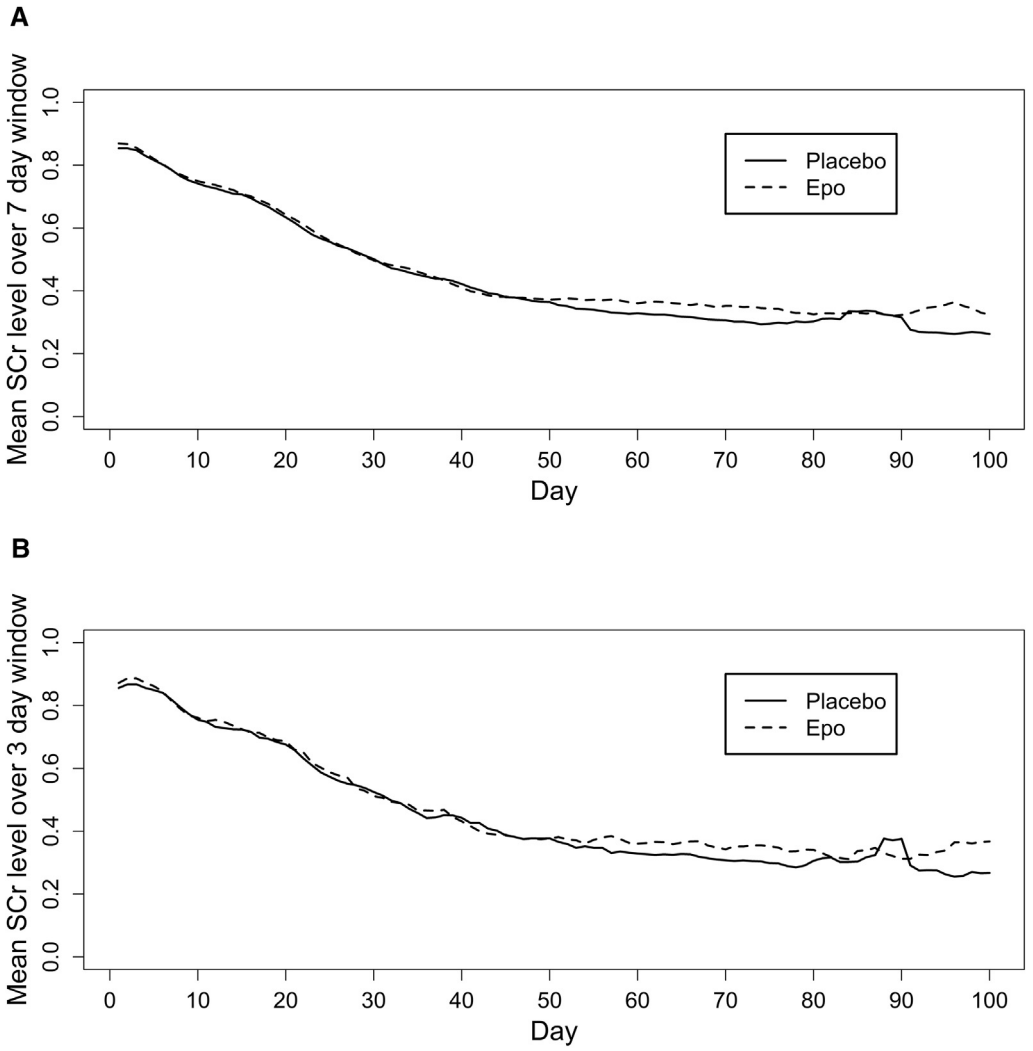

Figure 2. Mean creatinine levels over a rolling **A,** 7-day and **B,** 3-day window by treatment arm over time.

to rhEpo had lower independent adjusted odds of high SBP at 22-26 months cGA compared with those randomized to placebo. We did not observe any short-term kidney-related benefit by treatment for severe AKI, any AKI, or differences in SCr and cystatin C values during the first 2 postnatal weeks. We did not find differences in eGFR, urine ACR, or DBP by treatment arm at 22-26 months of cGA.

There are a few possible explanations for the findings of lower rates of high SBP in patients randomized to rhEpo. Interestingly, although there was a statistically significant independent difference in the categorical variable of SBP, there were no differences in SBP when evaluated as a continuous variable. Erythropoietin is made in the kidney and its presence has a role in normal kidney development. Thus, it is possible that high doses of rhEPO during the first postnatal weeks alter the kidney and vascular architectures such that the rates of long-term hypertension are improved. Alternatively, it is possible our finding of lower rates of high SBP in rhEpo group may be due to selection bias created, in context of a high number of participants in whom a blood pressure was not measured. Indeed, we found statistically significant differences, with a disproportionate number of subjects who were male (P = .05) and who received prenatal steroids (P = .06) in those with missing blood pressure measurements. Studies in other cohorts will be needed to validate or disprove this finding.

This study lends insight into the short- and long-term kidney outcomes in ELGANs using contemporary definitions of neonatal AKI and CKD. The overall prevalence of AKI in this cohort is similar to other studies in premature neonates.[24,31] We provide 2-year kidney-related data collected prospectively in a large multicenter cohort of ELGANs who survive NICU stay. We found that compared with the general 2 year old population, the participants had very high rates of abnormal kidney-related outcomes. Of the 191 participants who returned to follow-up and had blood, urine, and SBP and DBP measured, 47 of 191 (24.6%) had no abnormalities, and 144 of 191 (75.4%) had at least 1 kidney-related

Table V. 24-month kidney-related outcomes by treatment arm

Kidney-related outcome	Placebo N = 454	Epo N = 469	*P* value
eGFR value available, n (%)	179 (39.4%)	157 (33.5%)	.09
Median mL/min/1.73 m^2 (IQR)	101.3 (93.8, 113.8)	102.7 (96.6, 112.7)	.93
<90 mL/min/1.73 m^2, n (%)	29 (16.2%)	25 (15.9%)	.95
ACR available, n (%)	212 (46.7%)	223 (47.5%)	.81
Median, mg/g (IQR)	21.8 (13.4, 37.7)	22.0 (14.3, 38.2)	.78
≥30 mg/g, n (%)	78 (36.8%)	77 (34.5%)	.63
eGFR and ACR available, n (%)	131 (28.9%)	114 (24.3%)	.15
eGFR ≥90 and/or ACR <30, n (%)	125 (95.4%)	104 (91.2%)	.19
eGFR <90 and ACR ≥30, n (%)	6 (4.6%)	10 (8.8%)	
Hypertension value available, n (%)	258 (56.8%)	233 (49.7%)	.044
SBP			
SBP <90th percentile, n (%)	163 (63.2%)	168 (72.1%)	.1
SBP 90th-94th percentile, n (%)	29 (11.2%)	19 (8.1%)	
SBP ≥95th percentile, n (%)	66 (25.6%)	46 (19.7%)	
Median SBP (IQR) mm Hg	98.5 (90, 106.75)	97 (90, 104)	.21
DBP			
DBP <90th percentile, n (%)	117 (45.3%)	112 (48.1%)	.44
DBP 90th-94th percentile, n (%)	30 (11.6%)	33 (14.1%)	
DBP ≥95th percentile, n (%)	111 (43.0%)	88 (37.6%)	
Median DBP (IQR) mm Hg	58.0 (52.0, 65.8)	58.0 (50.0, 66.0)	.49

Hypertension defined as SBP >90th percentile for age and sex.

abnormality. Specifically, 67 of 191 (35.1%) had 1 kidney-related abnormality, 54 of 191 (28.3%) had 2 abnormalities, 21 of 191 (11.0%) had 3 abnormalities, and 2 of 191 (1.0%) had all 4 abnormalities. Recognizing that the methodology we used to assess kidney-related outcomes may be limited due to feasibility issues, these data speak to the significant risk of kidney disease in this population.

The strengths of this study are the size of the cohort, the robust number of SCr measurements available in the NICU, and the study design (double-blinded, randomized, placebo-controlled trial). It has high generalizability given the multicenter enrollment. Despite these strengths, we acknowledge the following limitations. First, not all neonates had SCr captured every day during the hospitalization; therefore, it is possible that the true AKI rate could be greater. Second, we acknowledge that although we performed study-related measurements that were optimized for a one-time visit, the methods to capture kidney-related outcomes (eGFR, spot urine ACR, and one-time manual blood pressure measurements) are not gold-standard methods to assess kidney-related outcomes. Furthermore, we acknowledge that the cutoff value of urine ACR we used (>30 mg/g), which is a surrogate for CKD in pediatric and adult populations, may not be applicable to this population. However, even when compared with a recent study of healthy 2-year-old children in the Netherlands,[28] the median ACR (21 vs 14 mg/g) and the rate of ACR >30 (36% vs 24%) are both greater in our cohort. We also acknowledge that a large number of patients did not have kidney-related metrics measured at the 2-year cGA time point.

In conclusion, this analysis shows that ELGANs who receive rhEPO in the first postnatal weeks have lower rates of high SBP at 2 years of age. We did not find any evidence that rhEPO improves the rates of AKI or kidney-related outcomes at around 2 years cGA, except that a greater proportion of those randomized to placebo had SBP >90th percentile. This study also confirms that the kidney-related short and long-term events are very common in ELGANs. Studies that use gold-standard measurements, studies that evaluate interventions to limit or prevent these outcomes, and evaluation of the most cost-effective methods for screening this high-risk population are greatly needed. In the meantime, neonatologists and pediatricians must discuss with families the risk of CKD in ELGANs. ■

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Reprint requests: David J. Askenazi, MD, MsPH, Division of Nephrology, Department of Pediatrics, University of Alabama at Birmingham, Lowder 502, 1600 7th Ave South, Birmingham, AL 35233. E-mail: daskenazi@peds.uab.edu

Data Statement

Data sharing statement available at www.jpeds.com.

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Appendix

List of additional members of the PENUT Trial Consortium

PENUT Primary Investigators

Sandra E. Juul[1], Bryan A. Comstock[1], Rajan Wadhawan[2], Dennis E. Mayock[1], Sherry E. Courtney[3], Tonya Robinson[4], Kaashif A. Ahmad[5], Ellen Bendel-Stenzel[6], Mariana Baserga[7], Edmund F. LaGamma[8], L. Corbin Downey[9], Raghavendra Rao[10], Nancy Fahim[10], Andrea Lampland[11], Ivan D. Frantz, III[12], Janine Y. Khan[13], Michael Weiss[14], Maureen M. Gilmore[15], Robin Ohls[16], Nishant Srinivasan[17], Jorge E. Perez[18], Victor McKay[19], Phuong T. Vu[1], Patrick J. Heagerty[1], and the PENUT Trial Consortium

PENUT Co-Investigators

Billy Thomas[3], Nahed Elhassan[3], Sarah Mulkey[3], Philip Dydynski[4], Vivek K. Vijayamadhavan[5], Neil Mulrooney[6], Bradley Yoder[7], Jordan S. Kase[8], Jennifer Check[9], Semsa Gogcu[9], Erin Osterholm[10], Sara Ramel[10], Catherine Bendel[10], Cheryl Gale[10], Thomas George[10], Michael Georgieff[10], Tate Gisslen[10], Sixto Guiang III[10], Anne Hall[10], Dana Johnson[10], Katie Pfister[10], Heather Podgorski[10], Kari Roberts[10], Erin Stepka[10], Melissa Engel[10], Heidi Kamrath[10], Johannah Scheurer[10], Angela Hanson[10], Katherine Satrom[10], Susan Pfister[10], Ann Simones[10], Erin Plummer[10], Elizabeth Zorn[10], Camilia R. Martin[12], Deirdre O'Reilly[12], Nicolas Porta[13], Catalina Bazacliu[14], Jonathan Williams[14], Dhanashree Rajderkar[14], Frances Northington[15], Raul Chavez Valdez[15], Sandra Beauman[16], Patel Saurabhkumar[17], Magaly Diaz-Barbosa[18], Arturo Serize[18], Jorge Jordan[18]

PENUT Research Coordinators

Debbie Ott[1], Ariana Franco Mora[1], Pamela Hedrick[1], Vicki Flynn[1], Amy Silvia[2], Bailey Clopp[2], John B. Feltner[2], Isabella Esposito[2], Stephanie Hauge[2], Samantha Nikirk[2], Andrea Purnell[3], Emilie Loy[3], Natalie Sikes[3], Melanie Mason[3], Jana McConnell[3], Tiffany Brown[3], Henry Harrison[3], Denise Pearson[3], Tammy Drake[3], Jocelyn Wright[3], Debra Walden[3], Annette Guy[3], Jennifer Nason[4], Morgan Talbot[4], Kristen Lee[4], Sarah Penny[4], Terri Boles[4], Melanie Drummond[5], Katy Kohlleppel[5], Charmaine Kathen[5], Brian Kaletka[6, 11], Shania Gonzales[6, 11], Cathy Worwa[6, 11], Molly Fisher[, 11], Tyler Richter[6, 11], Alexander Ginder[6, 11], Brixen Reich[7], Carrie Rau[7], Manndi Loertscher[7], Laura Bledsoe[7], Kandace McGrath[7], Kimberlee Weaver Lewis[7], Jill Burnett[7], Susan Schaefer[7], Karie Bird[7], Clare Giblin[8], Rita Daly[8], Kristi Lanier[9], Kelly Warden[9], Jenna Wassenaar[10], Jensina Ericksen[10], Bridget Davern[10], Mary Pat Osborne[10], Brittany Gregorich[10], Neha Talele[12], Evelyn Obregon[12], Tiglath Ziyeh[12], Molly Clarke[12], Rachel E Wegner[12], Palak Patel[12], Molly Schau[13], Annamarie Russow[13], Kelly Curry[14], Susan Sinnamon[14], Lisa Barnhart[14], Charlamaine Parkinson[15], Sandra Beauman[16], Mary Hanson[16], Elizabeth Kuan[16], Conra Backstrom Lacy[16], Edshelee M. Galvis[18], Susana Bombino[18], Denise Martinez[19], Suzi Bell[19], Corrie Long[19]

PENUT Follow-Up Personnel

Cathy Longa[2], Michael Westerveld[2], Stacy McConkey[2], Anne Hay[1], Niranjana Natarajan[1], Shari Gaudette[3], Sarah Cobb[3], Gregory Sharp[3], Elizabeth Schumacher[4], Leslie Schuschke[4], Charlotte Frey[5], Mario Fierro[5], Lois Gilmore[6], Pamela Lundequam[6], Ronald Hoekstra[6], Anastasia Ketko[6], Nina Perdue[6], Sean Cunningham[7], Kelly Stout[7], Becky Hall[7], Galina Morshedzadeh[7], Betsy Ostrander[7], Sarah Winter[7], Lauren Cox[8], Jordan S. Kase[8], Matthew A. Rainaldi[8], Sarah Hensley[9], Melissa Morris[9], Dia Roberts[9], Semsa Gogcu[9], Melissa Tuttle[9], Christopher Boys[10], Solveig Hultgren[10], Elizabeth I. Pierpont[10], Nancy Fahim[10], Tom George[10], Erin Osterholm[10], Michael Georgieff[10], Kelly E. King[10], Katherine Bataglia[11], Cathy Neis[11], Mark Bergeron[11], Cristina Miller[11], Cara Accomando[12], Jennifer Anne Gavin[12], Elizabeth Maczek[12], Susan Marakovitz[12], Aimee Knorr[12], Vincent C. Smith[12], Jane E. Stewart[12], Marie Weissbourd[13], Raye-Ann deRegnier[13], Nana Matoba[13], Shelly C. Heaton[12], Erika M. Cascio[12], Janet Brady[14], Suman Ghosh[14], Jessica Ditto[15], Mary Leppert[15], Jean Lowe[16], Janell Fuller[16], Tara DuPont[16], Robin Ohls[16], Pamela Kloska[17], Saurabh Patel[17], Lauren Carbonell[18], Anna Maria Patino-Fernandez[18] Carmen de Lerma[18], Susana Bombino[18], Arturo Serize[18], Kelly McDonough[18], Maiana De Cortada[18], Lacy Chavis[19], Jane Shannon[19]

University of Washington Data Coordinating Center

Bryan A. Comstock[1], Patrick J. Heagerty[1], Mark A. Konodi[1], Christopher Nefcy[1], Phuong T. Vu[1]

PENUT Follow-Up Committee

Karl C. K. Kuban[20], Jean R. Lowe[16], T. Michael O'Shea[21]

Radiology Committee

Manjiri Dighe[1], Todd Richards[1], Dennis W. W. Shaw[1], Colin Studholme[1], Christopher M. Traudt[1]

PENUT Executive Committee

Roberta Ballard[22], Bryan A. Comstock[1], Adam Hartman[23], Scott Janis[23], Sandra E. Juul[1], Dennis E. Mayock[1], T. Robin Ohls[16], Michael O'Shea[21]

DSMB

Ronnie Guillet[24], M. Bethany Ball[25], Hannah Glass[22], Ben Saville[26], Michael Schreiber[27]

1. University of Washington (Seattle, Washington)
2. AdventHealth for Children, (Orlando, Florida)
3. University of Arkansas for Medical Sciences (Little Rock, Arkansas)
4. University of Louisville, (Louisville, Kentucky)
5. Methodist Children's Hospital (San Antonio, Texas)
6. Children's Hospital and Clinics of Minnesota (Minneapolis, Minnesota)
7. University of Utah (Salt Lake City, Utah)
8. Maria Fareri Children's Hospital at Westchester Medical Center (Valhalla, New York)

9. Wake Forest School of Medicine (Winston-Salem, North Carolina)
10. University of Minnesota Masonic Children's Hospital (Minneapolis, Minnesota)
11. Children's Minnesota (St Paul, Minnesota)
12. Beth Israel Deaconess Medical Center (Boston, Massachusetts)
13. Prentice Women's Hospital (Chicago, Illinois)
14. University of Florida (Gainesville, Florida)
15. Johns Hopkins University (Baltimore, Maryland)
16. University of New Mexico (Albuquerque, New Mexico)
17. Children's Hospital of the University of Illinois (Chicago, Illinois)
18. South Miami Hospital (South Miami, Florida)
19. Johns Hopkins All Children's Hospital (St Petersburg, Florida)
20. Boston University Medical Center (Boston, Massachusetts)
21. University of North Carolina School of Medicine (Chapel Hill, North Carolina)
22. University of California San Francisco School of Medicine (San Francisco, California)
23. National Institute of Neurological Disorders and Stroke (Bethesda, Maryland)
24. University of Rochester Medical Center (Rochester, New York)
25. Stanford University and Lucile Packard Children's Hospital (Palo Alto, California)
26. Vanderbilt University Medical Center (Nashville, Tennessee)
27. University of Chicago (Chicago, Illinois)

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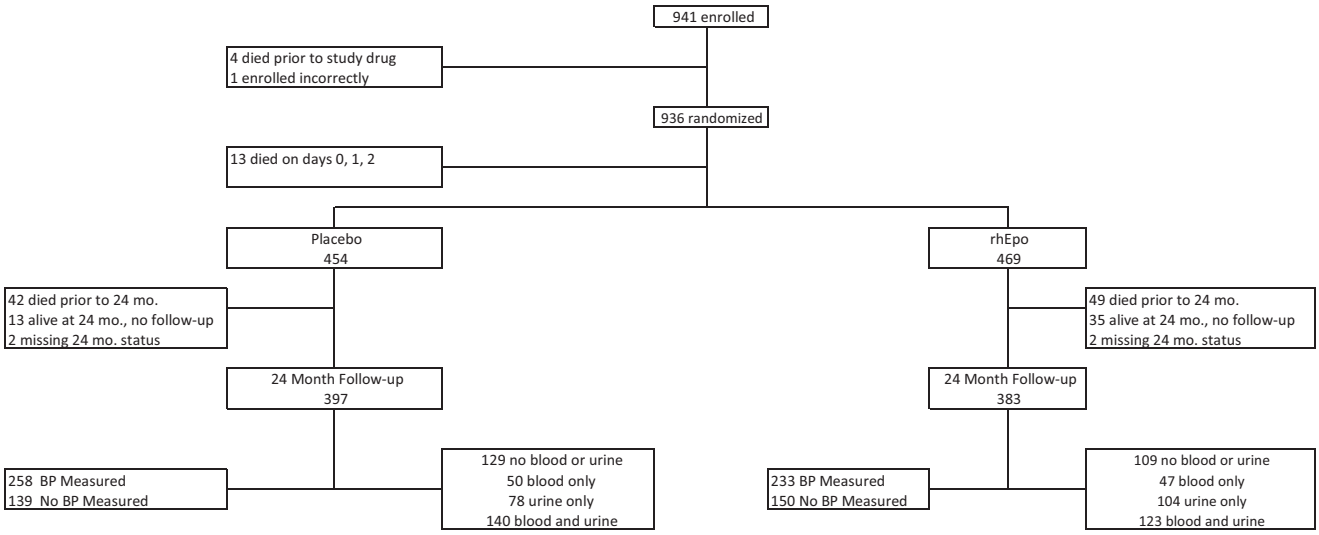

Figure 1. A total of 941 subjects were enrolled in the PENUT study. Of the 941, 18 were excluded from this study, as 4 died before study drug, 1 was enrolled incorrectly, and 13 died on days 0, 1, or 2, and we could not assign any kidney-related outcomes. Therefore, the final sample of participants for short-term outcomes in REPaIReD were the 923 who received study drug and were alive on day 3. Of the 923, 454 received placebo and 469 received rhEpo. At the 24-month follow-up, 780 infants were evaluated (397 in placebo and 383 in rhEpo) groups. The number who had blood/urine collected at the 24-month visit is described in the figure and in text. *BP*, blood pressure.

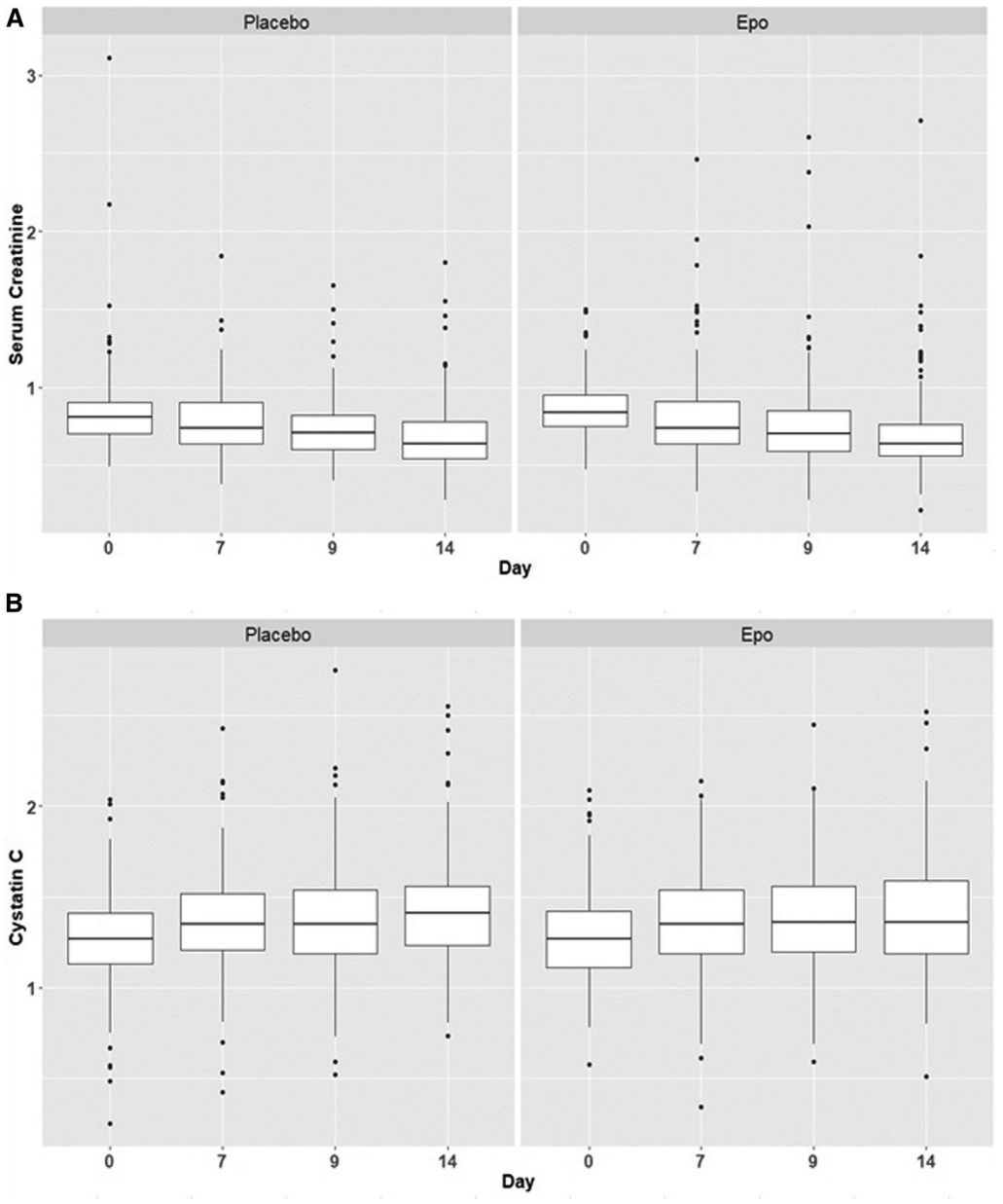

Figure 3. Core laboratory **A,** SCr and **B,** cystatin C (median and IQR) measurements on postnatal days 0, 7, 9, and 14 by treatment arm.

Table III. Central SCr and cystatin C values by treatment arm

Lab test	Treatment arm			*P* value
	All	Placebo	Epo	
n	624	309	315	
SCr, mean (SD) [n]				
Day 0	0.85 (0.20) [551]	0.83 (0.22) [273]	0.86 (0.17) [278]	.17
Day 7	0.79 (0.23) [514]	0.79 (0.20) [253]	0.79 (0.25) [261]	.99
Day 9	0.74 (0.23) [506]	0.73 (0.19) [251]	0.74 (0.26) [255]	.62
Day 14	0.68 (0.23) [457]	0.68 (0.21) [232]	0.69 (0.26) [225]	.49
Max	0.92 (0.25) [621]	0.91 (0.25) [308]	0.92 (0.25) [313]	.50
Change day 0-7	−0.06 (0.28) [473]	−0.05 (0.30) [233]	−0.08 (0.26) [240]	.28
Change day 0-9	−0.11 (0.27) [450]	−0.09 (0.26) [223]	−0.12 (0.28) [227]	.23
Change day 0-14	−0.17 (0.28) [430]	−0.16 (0.30) [216]	−0.18 (0.26) [214]	.47
Change day 7-9	−0.05 (0.15) [441]	−0.06 (0.15) [218]	−0.04 (0.14) [223]	.14
Change day 7-14	−0.10 (0.21) [413]	−0.11 (0.21) [210]	−0.09 (0.20) [203]	.37
Cystatin C				
Day 0	1.27 (0.23) [537]	1.27 (0.23) [269]	1.28 (0.23) [268]	.79
Day 7	1.38 (0.43) [505]	1.37 (0.28) [247]	1.39 (0.53) [258]	.66
Day 9	1.41 (0.56) [502]	1.38 (0.28) [248]	1.44 (0.73) [254]	.17
Day 14	1.42 (0.29) [454]	1.42 (0.29) [232]	1.41 (0.30) [222]	.54
Max	1.54 (0.51) [621]	1.52 (0.29) [308]	1.56 (0.66) [313]	.36
Change day 0-7	0.10 (0.44) [452]	0.09 (0.28) [223]	0.11 (0.55) [229]	.62
Change day 0-9	0.13 (0.59) [433]	0.10 (0.27) [216]	0.16 (0.79) [217]	.29
Change day 0-14	0.13 (0.31) [414]	0.16 (0.31) [212]	0.11 (0.31) [202]	.11
Change day 7-9	0.02 (0.24) [431]	0.01 (0.25) [210]	0.03 (0.24) [221]	.24
Change day 7-14	0.03 (0.49) [402]	0.04 (0.31) [204]	0.01 (0.62) [198]	.42

Table IV. GEE model estimates for severe AKI ~ treatment arm

AKI status	AKI groups	OR (95% CI)
Early AKI		
	NO vs 1/2/3	0.93 (0.62-1.41)
	NO or 1 vs 2/3	0.79 (0.32-1.95)
Middle AKI		
	NO vs 1/2/3	0.99 (0.69-1.44)
	NO or 1 vs 2/3	0.67 (0.38-1.20)
Late AKI		
	NO vs 1/2/3	1.04 (0.76-1.42)
	NO or 1 vs 2/3	0.86 (0.58-1.25)
Anytime AKI		
	NO vs 1/2/3	1.11 (0.83-1.48)
	NO or 1 vs 2/3	0.76 (0.54-1.07)

GEE models account for gestational age, sex, site, and sibship clustering.
Estimates shown only for treatment arm: Epo vs placebo.

Table VI. 24-month follow-up availability by treatment arm

Follow-up status	Placebo Number/total (%)	Epo Number/total (%)	*P* value
Died before 24 mo	42/454 (9.3%)	49/469 (10.4%)	.55
Alive at 24 mo	412/454 (90.7%)	420/469 (89.6%)	
Alive at 24 mo, no follow-up	13/412 (3.2%)	35/420 (8.3%)	.01
24-mo follow-up conducted	397/412 (96.4%)	383/420 (91.2%)	
Blood and urine	140/397 (35.3%)	123/383 (32.1%)	.1
Blood only	50/397 (12.6%)	47/383 (12.3%)	
Urine only	78/397 (19.6%)	104/383 (27.2%)	
Neither blood or urine	129/397 (32.5%)	109/383 (28.5%)	
Blood pressure measured	258/394 (65.5%)	234/383 (61.1%)	.24
Weight kg, mean (SD)	11.5 (1.8)	11.2 (1.8)	.48
Height cm, mean (SD)	84.7 (4.7)	85.0 (4.2)	.08

Table VII. Demographics of survivors by blood pressure availability by treatment arm

	Missing blood pressure		Available blood pressure		
	Placebo	rhEpo	Placebo	rhEpo	Interaction
n	N = 139	N = 150	N = 258	N = 233	*P* value
Male, n (%)	62 (44.6)	86 (57.3)	134 (51.9)	116 (49.8)	.048
Gestational age, n (%)					.28
24 wk	42 (30.2)	36 (24.0)	53 (20.5)	49 (21.0)	
25 wk	30 (21.6)	40 (26.7)	76 (29.5)	51 (21.9)	
26 wk	39 (28.1)	33 (22.0)	67 (26.0)	49 (21.0)	
27 wk	28 (20.1)	41 (27.3)	62 (24.0)	84 (36.1)	
Birth weight, g, mean (SD)	795.1 (170.1)	815.9 (180.8)	807.1 (187.6)	835.1 (196.7)	.85
Birth length, cm, mean (SD)	33.1 (2.5)	33 (3.1)	32.9 (2.8)	33.3 (3.1)	.25
Size for gestational age, n (%)					.57
Large	16 (11.5)	22 (14.7)	30 (11.6)	23 (9.9)	
Average	113 (81.3)	120 (80.0)	202 (78.3)	193 (82.8)	
Small	10 (7.2)	8 (5.3)	26 (10.1)	17 (7.3)	
Apgar 1 min, median (IQR)	4 (3, 5)	4 (1.5, 6)	4 (2, 6)	4 (2, 6)	.82
Apgar 5 min, median (IQR)	7 (5, 8)	7 (5, 8)	7 (5, 8)	7 (6, 8)	.09
Occipitofrontal circumference, cm, mean (SD)	23 (1.5)	23.1 (1.9)	23.2 (2.1)	23.3 (1.9)	.92
Number of fetuses, mean (SD)	1.3 (0.5)	1.3 (0.6)	1.3 (0.5)	1.3 (0.6)	.95
Prenatal steroids, n (%)	123 (89.8)	140 (94.6)	238 (94.1)	209 (90.9)	.06
1 dose	21 (17.1)	28 (20.0)	44 (18.5)	54 (25.8)	.08
2 doses	94 (76.4)	93 (66.4)	165 (69.3)	138 (66.0)	
3 doses	8 (6.5)	17 (12.1)	27 (11.3)	14 (6.7)	
Delivery room resuscitation, n (%)					
Any	136 (97.8)	145 (96.7)	253 (98.1)	221 (94.8)	.41
Oxygen	103 (74.1)	122 (81.3)	219 (84.9)	193 (82.8)	.13
Positive pressure	118 (84.9)	127 (84.7)	238 (92.2)	199 (85.4)	.12
Intubation	110 (79.1)	119 (79.3)	217 (84.1)	180 (77.3)	.23
Surfactant	72 (51.8)	72 (48.0)	136 (52.7)	117 (50.2)	.88
Chest compression	7 (5.0)	8 (5.3)	23 (8.9)	14 (6.0)	.44
Resuscitation drugs	4 (2.9)	5 (3.3)	7 (2.7)	6 (2.6)	.81

Table VIII. GEE regression estimates for treatment arm ~ CKD

Continuous outcomes	β (95% CI)
eGFR	0.27 (−3.08, 3.61)
ACR	−0.41 (−5.49, 4.67)
SBP	−1.58 (−3.72, 0.57)
DBP	−0.69 (−2.49, 1.11)
Binary outcomes	**OR (95% CI)**
eGFR <90	0.95 (0.52-1.77)
ACR ≥30	0.90 (0.59-1.36)
SBP >90th percentile	0.60 (0.39-0.92)
DBP >90th percentile	0.90 (0.61-1.33)

Each estimate represents Epo vs placebo for the given outcome variable after adjusting for site, gestational age while accounting for potential sibship clustering.

Table IX. Sensitivity analysis of differences in blood pressure if using lowest blood pressure vs average blood pressure

	Blood pressure using lowest value			Blood pressure using average value		
Blood pressure metric	**Placebo**	**rhEpo**	***P* value**	**Placebo***	**rhEpo†**	***P* value**
Hypertension value available, n (%)	258 (56.8)	233 (49.7)	.044	258 (56.8)	233 (49.7)	.044
SBP, n (%)						
SBP <90th percentile	163 (63.2)	168 (72.1)	.1	148 (57.4)	157 (67.4)	.06
SBP 90th-94th percentile	29 (11.2)	19 (8.1)		33 (12.8)	21 (9.0)	
SBP ≥95th percentile	66 (25.6)	46 (19.7)		77 (29.8)	55 (23.6)	
Median SBP (IQR) mm Hg	98.5 (90, 106.75)	97 (90, 104)	.21	98.75 (92, 107)	96 (90, 104)	.23
DBP, n (%)						
DBP <90th percentile	117 (45.3)	112 (48.1)	.44	102 (39.5)	97 (41.6)	.36
DBP 90th-94th percentile	30 (11.6)	33 (14.1)		27 (10.5)	32 (13.7)	
DBP ≥95th percentile	111 (43.0)	88 (37.6)		129 (50.0)	104 (44.6)	
Median DBP (IQR) mm Hg	58.0 (52.0, 65.8)	58.0 (50.0, 66.0)	.49	60.0 (53.1, 67.5)	59.5 (52.0, 65.0)	.29

*A total of 155 of 258 (60.1%) in the placebo group had more than 1 blood pressure reading.
†A total of 134 of 233 (57.5%) in the rhEpo group had more than 1 blood pressure reading.