

# Delayed Umbilical Cord Clamping is Not Associated with Acute Kidney Injury in Very Low Birth Weight Neonates

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## Abstract

### Keywords

- ▶ acute kidney injury
- ▶ delayed cord clamping
- ▶ umbilical cord milking
- ▶ very low birth weight
- ▶ premature
- ▶ preterm birth
- ▶ neonate

**Objective** This study aimed to determine if delayed cord clamping (DCC) is associated with a reduction in neonatal acute kidney injury (AKI).

**Study Design** A retrospective single-center cohort study of 278 very low birth weight (VLBW) neonates was performed to compare the incidence of AKI in the following groups: immediate cord clamping (ICC), DCC, and umbilical cord milking. AKI was diagnosed by the modified neonatal Kidney Diseases and Improving Global Outcomes (KDIGO) definition.

**Results** The incidence of AKI in the first week was 20.1% with no difference between groups ( $p = 0.78$ ). After adjustment for potential confounders, the odds of developing AKI, following DCC, compared with ICC was 0.93 (confidence interval [CI]: 0.46–1.86) with no reduction in the stage of AKI between groups.

**Conclusion** In this study, DCC was not associated with a reduced rate of AKI in VLBW neonates. However, the data suggest that DCC is also not harmful to the kidneys, further supporting the safety of DCC in VLBW neonates.

After birth, preterm newborns undergo a dynamic postnatal transition characterized by significant circulatory and respiratory system alterations. This postnatal transition period may be augmented by delayed umbilical cord clamping (DCC) for 30 to 60 seconds, a placental-to-neonatal transfusion strategy associated with increased newborn blood volumes, arterial oxygen content, cardiac output, and oxygen delivery.<sup>1</sup> The practice of DCC among preterm births endorsed by the American Academy of Pediatrics,<sup>2</sup> the American College of Obstetrics and Gynecology,<sup>3</sup> and International Liaison Committee on Resuscitation<sup>4</sup> is supported by findings of a recent systematic review and meta-analysis by Fogarty et al which included 18 randomized controlled trials (2,834 infants born <37 weeks' gestation)

and demonstrated that DCC reduced hospital mortality compared with immediate cord clamping (ICC).<sup>5</sup> An alternative to DCC is umbilical cord milking (UCM) in which the intact unclamped umbilical cord is stripped three to four times toward the neonate to promote blood transfer before the cord is clamped.<sup>1</sup> While DCC and UCM appear to be safe in preterm neonates, the impact of these placental transfusion strategies on numerous common preterm neonatal morbidities, including kidney dysfunction, remains unknown.<sup>6,7</sup>

In 2013, the National Institutes of Health recognized the need for a better understanding of acute kidney injury (AKI) in neonates and convened a workshop to discuss controversies surrounding this neonatal morbidity.<sup>8</sup> The result of this

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workshop was a proposal to utilize the Kidney Diseases and Improving Global Outcomes (KDIGO) modified neonatal AKI criteria. The committee recognized the shortcomings of this definition in neonates including the effect of maternal creatinine on early neonatal creatinine values. Therefore, the definition of AKI requires a rise in creatinine after birth (0.3 mg/dL in 48 hours) not an elevated creatinine alone just after birth. Since that time, attention has been focused on the short- and long-term complications of neonatal AKI utilizing the KDIGO's definition of AKI, including several publications from the Neonatal Kidney Collaborative's retrospective study AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates).<sup>9</sup> This multicenter, multinational study demonstrated that neonatal AKI is independently associated with poor short-term outcomes, such as death and length of stay and the risk factors for AKI vary depending on both gestational and postnatal age.<sup>10,11</sup> Many of the risk factors for neonatal AKI in the first week after birth are related to prerenal causes of AKI, including respiratory distress and mechanical ventilation, hypotension, sepsis, and a hemodynamically significant patent ductus arteriosus.<sup>12</sup> DCC may affect several of these prerenal AKI causes, since DCC increases circulating blood volume during transitional physiology at birth and decreases rates of neonatal anemia.<sup>5,13</sup> With no current medications available to treat neonatal AKI, DCC may provide a preventative strategy to reduce the incidence of AKI.

The aim of this study was to determine the relationship of DCC and neonatal AKI in the first week after birth. We hypothesized that DCC would be associated with a lower incidence of AKI compared with ICC.

## Materials and Methods

A retrospective, single-center cohort study of very low birth weight (VLBW) neonates was conducted at the University of Virginia (UVA) neonatal intensive care unit (NICU) from January 1, 2013 to December 31, 2016. During this period, the type of umbilical cord management was determined by the clinician and the decision to use ICC, DCC, or UCM was highly variable between clinicians.

For inclusion, neonates had to be born at UVA and weigh <1,500 g at birth. Neonates missing the data to classify their type of umbilical cord care, including those born at other institutions and those with a combination of cord care, were excluded. The primary exposure was DCC, defined as not clamping the umbilical cord for 30 to 90 seconds after delivery, compared with the ICC group, defined as cord clamping that occurred <15 seconds after birth. UCM was performed at the discretion of the provider and most frequently in neonates born with poor respiratory effort or tone who were deemed to require immediate resuscitation by the neonatal team. We elected to examine UCM as a separate exposure and defined it as milking a 20-cm segment of umbilical cord three to four times, while the placenta was still attached.

The outcome of interest was AKI defined by the modified KDIGO neonatal AKI staging system which is based on serum creatinine (sCr) and urine output (UOP) values (–Table 1).<sup>14</sup> AKI was assessed during the first 7 days after birth. Mea-

**Table 1** Modified KDIGO neonatal AKI staging

Stage	Serum creatinine	Urine output
0	No change in sCr or rise < 0.3 mg/dL	No changes or decrease but still > 1 mL/kg/h
1	sCr rise $\geq$ 0.3 mg/dL within 48 hours or sCr rise $\geq$ 1.5–1.9 $\times$ reference sCr <sup>a</sup> within 7 days	> 0.5 and $\leq$ 1 mL/kg/h
2	sCr rise $\geq$ 2 to 2.9 $\times$ reference sCr <sup>a</sup>	> 0.3 and $\leq$ 0.5 mL/kg/h
3	sCr rise $\geq$ 3 $\times$ reference sCr <sup>a</sup> or sCr $\geq$ 2.5 mg/dL <sup>b</sup> or receipt of dialysis	$\leq$ 0.3 mL/kg/h or Anuria

Abbreviations: AKI, acute kidney injury; KDIGO, kidney diseases and improving global outcomes; sCr, serum creatinine.

Note: KDIGO neonatal AKI definition. Baseline creatinine was the lowest previous value.

<sup>a</sup>Reference sCr is the lowest prior sCr measurement.

<sup>b</sup>This is lower than the original KDIGO definition as a sCr of 2.5 mg/dL in neonates suggests a glomerular filtration rate < 10 mL/min/1.73 m<sup>2</sup>.

surement of sCr was performed at the UVA clinical laboratory using the alkaline picrate (Jaffe) method traceable to isotope dilution mass spectrometry. Bedside nurses assessed UOP in 6-hour intervals by weighing diapers.

Perinatal data collected from each neonate included gestational age, sex, delivery type, multiple gestation, Apgar's scores at 1 and 5 minutes, and indomethacin and gentamicin exposure. To assess the degree of illness on admission, Clinical Risk Index for Babies (CRIB)-II scores were collected. Maternal data on preeclampsia, chorioamnionitis, magnesium, and betamethasone exposure were also collected. The presence of intraventricular hemorrhage (IVH;  $\geq$  Papile's grade 1), necrotizing enterocolitis ( $\geq$  Bell's stage 2) and patent ductus arteriosus requiring medication or surgical treatment were recorded. To assess for clinically significant hypotension, exposure to vasopressor medications (dopamine, dobutamine, epinephrine, norepinephrine, and vasopressin) was recorded. To assess blood volume status an initial hematocrit was typically collected within an hour after birth and a follow-up hematocrit within 48 to 72 hours. The number of blood transfusions in the first 28 days was also collected.

All data were gathered from the neonate's electronic medical record and both cord management and laboratory testing were performed at the discretion of the primary team. The sCr measurements were obtained as part of the standard basic metabolic panel that was obtained daily for the first 7 days after birth.

Statistical analysis for continuous variables was summarized by the median and lower and upper quartiles; the nonparametric Kruskal–Wallis test was used to compare these characteristics across groups. Categorical patient demographic and medical characteristics were tabulated and compared among cord care groups using Chi-squared tests. The Chi-squared test was also used to compare the “early AKI” and “any AKI” outcomes among cord-care groups. Logistic regression was used to identify significant predictors for each definition of AKI. Several

methods of adjustment were used to account for differing sets of significant predictors for the different definitions. Additionally, for each definition of AKI, stepwise logistic regression was used to select the variables to be included in the model. In addition, logistic regression was used to estimate this odds ratio after adjusting for each individual maternal and neonatal factor. Bayesian model averaging was used to combine these estimates into a single odds ratio estimate. Analyses were performed in SAS version 9.4 (Cary, NC).

## Results

During the study period, 299 VLBW neonates were born at UVA. Of the 299 eligible patients, 21 were excluded due to missing data or the use of combined cord management techniques prior to resuscitation (►Fig. 1). For the 278 included in the analysis, 45% received DCC, 42% had ICC, and 13% received UCM. The birth weight and gestational age did not differ among the three groups (►Table 2). The UCM group had a nonstatistically significant higher percentage of extremely preterm infants ( $\leq 27^{6/7}$  weeks: UCM = 59%, ICC = 53%, DCC = 43%;  $p = 0.15$ ), but statistically significant lower 1- ( $p < 0.001$ ) and 5-minute Apgar's scores ( $p = 0.002$ ) and more patients with IVH (43%,  $p = 0.04$ ). The ICC group received more days of gentamicin and the UCM group had more exposure to vasopressor medications. There were no statistically significant differences in CRIB-II scores between groups (DCC = 9 [range, 6–11], ICC = 9 [range, 6–13], and UCM = 10 [7–13],  $p = 0.105$ ).

The initial hematocrit (obtained  $< 4$  hours after birth) was the highest in the ICC group (ICC = 45.7, DCC = 44.6;  $p = 0.02$ ). However, by 48 to 72 hours, the DCC group had the highest hematocrit (ICC = 42.0, DCC = 43.5;  $p = 0.051$ ). In the first 28 days of hospitalization, the DCC group required the fewest number of transfusions ( $p = 0.01$ ). With regards to renal function, the initial sCr did not differ (0.7 mg/dL) and the peak sCr was not different (0.8–0.9 mg/dL,  $p = 0.58$ ) among the three groups.

The primary outcome of AKI occurred in 20.1% ( $n = 56$ ) of neonates. The three cohorts did not differ in AKI incidence (DCC = 20%, ICC = 21.6%, UCM = 16.2%;  $p = 0.779$ , ►Table 3). Of the 56 neonates with AKI, only 13 had changes in both sCr

and UOP that qualified for AKI. When breaking down the diagnosis of AKI by sCr or UOP, there were again no differences in three groups. Of the 56 patients with AKI, the majority experienced stage-1 injury ( $n = 50$ ), while only six patients had stage-2 injury. There were no statistical differences in severity of injury between the three groups ( $p = 0.36$ ). Additionally, the AKI incidence for the entire hospitalization was not different between the three groups (DCC = 30.4%, ICC = 36.2%, UCM = 35.1%;  $p = 0.62$ ).

Univariate logistic regression analysis comparing DCC to ICC identified birth weight and the number of blood transfusions within 28 days as significant for every definition of AKI. Subsequent multivariate logistic regression analysis, stepwise logistic regression, and Bayesian's modeling averaging showed no significant difference in the odds of developing AKI when comparing the DCC and ICC groups (►Table 4).

## Discussion

In this retrospective cohort study, we compared the outcome of AKI between VLBW infants who had different cord management styles immediately after birth. Contrary to our hypothesis, the DCC group did not have less AKI in the first week of age when compared with the ICC group. Even after adjusting for significant AKI risk factors, there was no difference between the groups. Although nearly all pediatric and obstetric national and international organizations have begun to recommend DCC, they did so with very little data on how DCC affects kidney function. The current study data provide evidence of safety for DCC from a kidney perspective in VLBW infants who typically have an AKI rate of 29% during their NICU hospitalization.<sup>10</sup> With recent evidence from pediatric studies that fluid overload increases the risk of AKI<sup>15</sup> and with DCC providing nearly an equivalent of a blood transfusion, this is an important addition to the safety profile of DCC that has not been analyzed in prior studies.

Systematic reviews summarizing the exponential increase in publications and research on DCC compared with ICC in the past 10 years have focused primarily on comparing the risks of mortality and the preterm morbidities of the cerebral, cardiovascular, and hematologic systems.<sup>5</sup> Few studies have examined the effect on kidney function when comparing ICC to DCC strategies with no studies assessing the risk for AKI. In 1966, Oh and colleagues evaluated a group of female term infants comparing 22 ICC infants to 47 DCC infants.<sup>16</sup> They found that, in the first 12 hours after birth, the DCC infants had higher UOP and more effective renal blood flow compared with the ICC group. There was a positive correlation between DCC and glomerular filtration rates; however, this did not reach statistical significance. In our study, we similarly did not find any difference in initial sCr's in the three groups, and we also did not have any difference in AKI diagnosis by UOP. It is important to note that the cohort by Oh et al was the study of full term, not preterm, and 50 years separates the studies, making it difficult to make direct comparisons. In the future, new technologies, such as renal near-infrared spectroscopy and functional echocardiography could be used as surrogates for effective renal blood flow in the first 48 hours after birth to compare the effects of DCC, ICC, and UCM on renal blood flow.

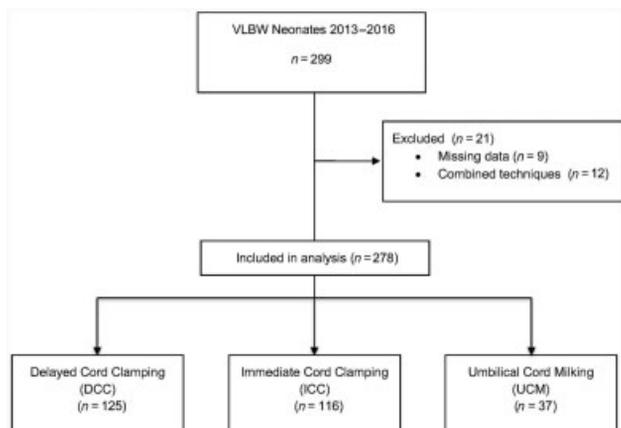


Fig. 1 Study flow chart. VLBW, very low birth weight.

**Table 2** Patients' characteristics

	DCC n = 125	ICC n = 116	UCM n = 37	p-Value
<b>Maternal factors</b>				
Maternal age (wk)	28 (25–34)	27 (23–32)	29 (24–35)	0.07
C-section	87 (70%)	82 (71%)	28 (76%)	0.77
Multiple birth	38 (30%)	33 (28%)	6 (16%)	0.23
Chorioamnionitis	3 (2%)	3 (2%)	0 (0%)	0.62
Preeclampsia	35 (28%)	20 (17%)	9 (24%)	0.14
Magnesium	99 (79%)	91 (78%)	27 (73%)	0.72
Betamethasone doses				0.07
0	7 (6%)	10 (9%)	5 (4%)	
1	30 (24%)	38 (33%)	6 (16%)	
2	88 (70%)	67 (58%)	26 (70%)	
<b>Neonatal factors</b>				
Gestational age (wk)				0.15
≤ 27 6/7	54 (43%)	61 (53%)	22 (59%)	
28–31 6/7	58 (46%)	38 (33%)	12 (32%)	
> 31 6/7	13 (10%)	17 (15%)	3 (8%)	
Birth weight (g)				0.31
< 750	24 (19%)	30 (26%)	12 (32%)	
750–1,000	32 (26%)	26 (22%)	11 (30%)	
> 1,000	69 (55%)	60 (52%)	14 (38%)	
Male	69 (55%)	63 (54%)	18 (49%)	0.78
CRIB-II score	9 (6–11)	9 (6–13)	10 (7–13)	0.105
PDA (treated)	9 (7.2%)	13 (11.2%)	7 (18.9%)	0.115
NEC	2 (2%)	6 (5%)	2 (5%)	0.27
IVH (any)	28 (22%)	31 (27%)	16 (43%)	0.04
Vasopressors (yes/no)	9 (7%)	18 (15%)	10 (27%)	0.005
Apgar's score (1 min)	7 (5–7)	5 (2–7)	4 (2–6)	<0.001
Apgar's score (5 min)	8 (6–8)	7 (6–8)	6 (5–7)	0.002
<b>DCC outcomes</b>				
Hct (birth)	44.6 (40.8–50.4)	45.7 (41.4–50.2)	42.8 (38.7–46.2)	0.020
Hct (48–72 h)	43.5 (38.6–47.9)	42.0 (36.7–47.5)	39.9 (38.4–42.3)	0.051
No. of blood transfusions < 28 days	0 (0–2)	1 (0–5)	1 (0–4)	0.01
<b>Kidney outcomes</b>				
Initial creatinine	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.26
Peak creatinine	0.9 (0.7–1.0)	0.8 (0.8–1.0)	0.9 (0.8–1.1)	0.58
Indomethacin dose	0 (0–0.3)	0 (0–0.3)	0 (0–0.3)	0.14
Gentamicin (no. of doses)	2 (0–4)	4 (2–4)	2 (2–6)	0.029

Abbreviations: c-section, caesarean section; CRIB, clinical risk index for babies; DCC, delayed cord clamping; ICC, immediate cord clamping; Hct, hematocrit; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; sCr, serum creatinine; UCM, umbilical cord milking. Note: Statistical analysis values reported as median (interquartile range) or n (%).

Previous studies, while not including AKI or sCr as outcomes, have reported UOP data related to different cord management techniques. In 2009, Hosono et al compared the UOP of 40 VLBW infants and found that the UOP was

higher in the UCM group for each of the first 3 days after birth compared with the ICC group.<sup>17</sup> The sCr measurements were not reported, making it impossible to determine if the enrolled infants developed AKI. In 2015, a study comparing DCC to UCM,

**Table 3** AKI outcomes

	DCC n = 125 (%)	ICC n = 116 (%)	UCM n = 37 (%)	p-Value (DCC–ICC)	p-Value (3 groups)
AKI (<7 days)					
AKI by sCr	18 (14.4%)	16 (13.8%)	5 (13.5%)	0.892	0.986
AKI by UOP	13 (10.4%)	15 (12.9%)	2 (5.4%)	0.540	0.430
AKI by both	6 (4.8%)	6 (5.2%)	1 (2.7%)	0.894	0.822
AKI by either	25 (20.0%)	25 (21.6%)	6 (16.2%)	0.767	0.779
Stage 1	22 (17.6%)	24 (20.7%)	4 (10.8%)	0.553	0.356
Stage 2	3 (2.4%)	1 (0.9%)	2 (5.4%)		
Stage 3	0 (0%)	0 (0%)	0 (0%)		

Abbreviations: AKI, acute kidney injury; DCC, delayed cord clamping; ICC, immediate cord clamping; sCr, serum creatinine; UCM, umbilical cord milking; UOP, urine output.

**Table 4** Regression analysis comparing DCC to ICC

	Unadjusted	Adjusted	Adjusted by stepwise	Adjusted by BMA
Early AKI				
AKI by sCr	0.95 (0.46–0.97)	0.68 (0.30–1.52)	0.81 (0.37–1.76)	0.77 (0.34–1.75)
AKI by UOP	1.28 (0.58–2.82)	1.11 (0.48–2.52)	1.32 (0.57–3.04)	1.26 (0.56–2.83)
AKI by Both	1.08 (0.34–3.45)	0.48 (0.19–1.21)	0.97 (0.28–3.43)	0.96 (0.28–3.29)
AKI by Either	1.10 (0.59–2.05)	0.86 (0.44–1.69)	0.89 (0.45–1.75)	0.93 (0.46–1.86)

Abbreviations: AKI, acute kidney injury; DCC, delayed cord clamping; ICC, immediate cord clamping; sCr, serum creatinine; UOP, urine output; BMA, Bayesian model averaging.

by Katheria et al, reported that infants in the UCM group had higher UOP compared with the DCC group in the first 24 hours after birth (4.42 vs. 3.99 mL/kg/h,  $p < 0.05$ ).<sup>18</sup> This statistically, but not clinically, significant difference does not reach the minimum rate of UOP to qualify for the KDIGO neonatal AKI criteria. We did not assess the total UOP in our study but did evaluate for clinically significant decreases in UOP over 6-hour stretches during the first week and did not find a difference between the DCC, ICC, or UCM groups.

While AKI rates were not different, based on the different cord management groups we studied, potential explanations for these findings warranted further discussion. If AKI is influenced by placental-to-neonatal transfusion volume, then AKI rates may have been unaffected because of insufficient DCC transfusion volumes, an explanation raised by the higher postdelivery hematocrits in the ICC group. However, by 48 to 72 hours the DCC group had higher hematocrits and also required less blood transfusion, findings which suggest that the DCC transfusion volumes were not the reason for lack of a difference in AKI rates. Another unaccounted factor that may have resulted in different AKI rates in our study was the use of medications other than indomethacin. First, different caffeine administration rates, previously shown to be protective of AKI in VLBW infants<sup>19,20</sup> may have impacted AKI rates. Second, higher rates of gentamicin doses received in the first week for the ICC group may have increased the prevalence of AKI in this group disproportionately to the DCC group making it difficult to detect an effect of cord clamping. While our study did not demonstrate that DCC is associated with less AKI compared

with ICC, our study supports a lack of harm associated with DCC in preterm VLBW infants. Because placental transfusion strategies have become the standard of care, the question becomes which placental transfusion strategy (DCC vs. UCM) confers improved kidney outcomes in preterm infants.

When evaluating the UCM group it is important to know that the clinical indication for infants receiving UCM was they were perceived to be “too sick” to delay the neonatal resuscitation during DCC. Therefore, the UCM cohort in our study should be viewed as the sickest group, evidenced by the lowest Apgar’s scores, lower birth weights, higher use of vasopressors, higher CRIB-II scores, and lower gestational ages compared with the other groups. Despite being the highest risk group for AKI compared with the ICC and DCC groups, AKI rates were not significantly different in UCM group which suggests that UCM may have “rescued” or preserved renal blood flow, resulting in similar kidney outcomes in these infants. Future studies comparing DCC to UCM in infants who require active resuscitation after delivery, who would typically be most at risk for AKI, should consider evaluating renal function and UOP data to determine which placental transfusion strategy results in improved kidney outcomes.

## Limitations

This study has several limitations, primarily due to the retrospective study design. First, AKI assessment was limited by the number of sCr’s obtained by the clinician’s typical practice. Second, the assessment of urine output in neonates

is challenging and is done through weighing of diapers, potentially including stool, and thus artificially increasing the suspected urine output and allowing for “missed” cases of AKI. Third, the type of cord management was also at the clinician’s discretion and, although there were small overt group differences, subtle biases may have also been present that could have affected outcomes. Fourth, we did not collect neonatal information on sepsis, but we did collect data on clinically significant hypotension requiring vasopressors and this would be the most common cause of AKI secondary to sepsis. While sepsis has been shown to influence rates of AKI, typically it is more common in smaller and lower gestational age neonates, which were equally distributed between our three cohorts of patients. Although vasopressor exposure was different in the groups, we were unable to assess the adequacy of hypotensive therapies. Lastly, the modified KDIGO definition for neonatal AKI has been challenged, particularly in the preterm group given their issues with kidney immaturity and maternal sCr.<sup>21</sup> As the neonatal AKI definition evolves, long-term and larger studies should assess whether DCC provides renal protective effects in preterm neonates.

## Conclusion

In conclusion, in this retrospective study, the effect of various cord management styles was evaluated to determine the effect on kidney function in a large cohort of preterm neonates. No significant differences were found in AKI rates in the first week after birth between the DCC, UCM, and ICC groups. In our cohort, the increased hematocrit at 48 hours of age and decreased number of blood transfusions in the DCC group compared with the ICC group suggest that DCC was more effective in enhancing circulating blood volume. Overall, since the AKI incidence was not increased in the DCC or UCM groups, DCC and UCM appear safe from a neonatal kidney perspective. If further prospective, randomized trials are performed comparing DCC to UCM, kidney function data, both short (AKI and UOP) and long term (function and chronic kidney disease), should be included as a priori outcomes.

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### Conflict of Interest

J.R.C. is co-owner of Sindri Technologies, LLC.

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