NICHD

NEONATAL RESEARCH NETWORK

Effect of Darbepoetin on Respiratory Outcomes through 2 Years' Corrected Age in Preterm Infants:

Secondary Results of the NICHD Neonatal Research Network (NRN) Darbe Trial

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Disclosures

- Speaker: Erik Jensen

- Dr. Jensen has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

- This presentation will involve discussion of the off-label, investigational use of darbepoetin
  - IND #100138, NCT03169881

Darbepoetin

- Darbepoetin alfa (Darbe) is a protein analog of human erythropoietin (EPO). Its longer half-life allows for once weekly dosing.
- FDA approved for treatment of anemia in chronic kidney disease and myelosuppressive chemotherapy.
- Trials in preterm infants show increased hematocrit, decreased red blood cell (RBC) transfusions, decreased donor exposures.
- May have beneficial non-hematopoietic effects.

NRN Darbepoetin Trial for Neuroprotection

P	• 650 infants born $23^{0/7}$ to $28^{6/7}$ weeks' gestation • Enrolled ≤24hr of age between 2017-2019 (f/u through 2022)
I	• Darbepoetin 10µg/kg weekly (IV or SC) through 35 weeks' PMA
C	• Placebo (IV) or sham injection (SC)
All	• Parenteral or enteral iron supplementation per study guidelines • Restrictive protocol for red blood cell transfusions
O	• Primary: Bayley III composite cognitive score at 22-26 months • Secondary: Multiple pre-specified outcomes

Darbepoetin reduced grade 2-3 BPD

Results presented at the 2023 PAS Annual Meeting (Ohls et al. abstract #2150.4)

Outcome	Darbepoetin	Placebo	Adjusted RR† (95% CI)
Grade 2-3 BPD in survivors to 36 weeks' PMA*	35% 91/261	46% 128/277	0.78 (0.64 - 0.96)

† GEE models adjusted for GA stratum, center, and familial clustering

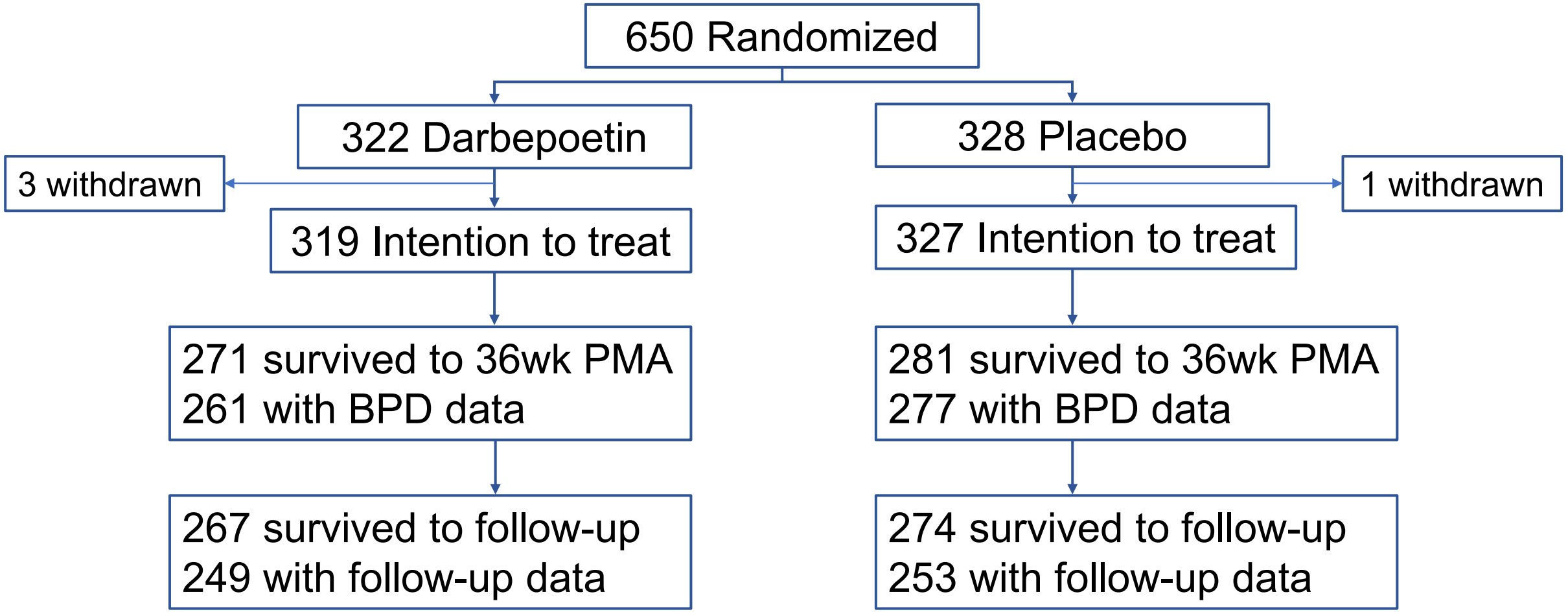
* Defined as treatment with nasal cannula >2L/min, non-invasive positive airway pressure, or invasive mechanical ventilation at 36 weeks' PMA (Jensen et al. AJRCCM 2019)

Design and Methods

- Post-hoc analysis of data from the NRN Darbe Trial
- Compared respiratory outcomes among trial participants using
  - Darbe Trial data
  - NRN Birth Registry (aka Generic Database)
  - NRN Follow-up Registry
- Mediation analyses examined whether differences in
  - RBC transfusion number through 36 weeks' PMA, *or*
  - Calculated red blood cell mass at 42 days of age

  may have contributed to the observed reduction in BPD

Trial Flow Diagram



93% of randomized infants (607/650) had known death or 2-year respiratory outcome data

Participant characteristics

	Darbe (n=322)	Placebo (n=328)
Gestational age, wk - mean (SD)	26.2 (1.7)	26.2 (1.6)
Birthweight, g - mean (SD)	838 (253)	822 (239)
Female	52%	49%
Antenatal steroids	93%	93%
Multiple birth	24%	29%
Chorioamnionitis (histological)	8%	12%
Delayed cord clamping or milking	40%	41%
Hematocrit, % - mean (SD)	43 (7)	43 (7)
Surfactant	81%	84%
Invasive ventilation at 24hr	59%	55%

Death or Grade 2-3 BPD

Outcome	Darbe	Placebo	Adjusted RR (95% CI)*
Grade 2-3 BPD in survivors to 36wk PMA	35% 91/261	46% 128/277	0.78 (0.64 - 0.96)
Death or grade 2-3 BPD at 36wk PMA	45% 139/309	54% 174/323	0.85 (0.73 - 0.99)
Died prior to 36wk PMA	15% 48/319	14% 46/327	1.04 (0.73 - 1.49)

* GEE models adjusted for GA stratum, center, and familial clustering

Duration of respiratory support

Outcome	Darbe (n=266)	Placebo (n=273)	Adjusted mean difference (95% CI)
Days of invasive ventilation at 120d of age	20 (26)	25 (29)	-4.3 (-8.1 to -0.40)
Days of positive airway pressure at 120d of age	50 (30)	57 (31)	-5.2 (-9.3 to -1.04)
Days of supplemental O_2 at 120d of age	63 (41)	70 (40)	-6.3 (-12.0 to -0.63)

Unadjusted data are mean (SD). GEE models adjusted for GA stratum, center, and familial clustering

In-hospital respiratory outcomes

Outcome	Darbe	Placebo	Adjusted RR* (95% CI)
Treatment for PDA	26% 68/266	33% 91/274	0.75 (0.55 to 1.03)
Systemic steroids for BPD	27% 86/319	30% 96/325	0.88 (0.70 to 1.11)
Discharge on home O_2	37% 92/249	38% 98/258	0.96 (0.78 to 1.17)
Discharge on diuretics or bronchodilators	21% 51/249	23% 58/258	0.92 (0.63 to 1.34)

*GEE models adjusted for GA stratum, center, and familial clustering

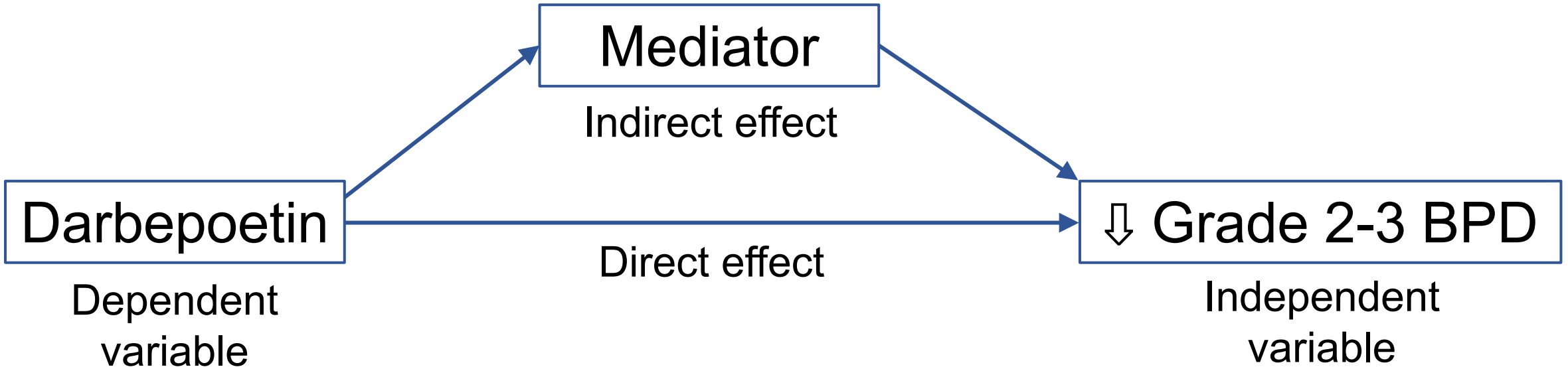
Respiratory outcomes at 22-26mo corrected age

Outcome	Darbe	Placebo	Adjusted RR* (95% CI)
Inhaled medication(s) within past 3 months	31% 78/249	27% 68/253	1.19 (0.90 - 1.56)
Home O_2 at follow-up	5% 12/249	5% 13/253	Not calculated Low & similar event rate
Ventilator or CPAP use at follow-up	2% 4/249	2% 4/253	Not calculated Low & similar event rate
Readmission for respiratory reasons	19% 48/249	23% 57/253	0.97 (0.69 - 1.37)

*GEE models adjusted for GA stratum, center, and familial clustering

Mediation analysis

- Decomposes exposure-outcome relationships into direct (treatment) and indirect (causal intermediary) effects
- Total effect = direct + indirect effects
- Provides insight into treatment mechanisms



Possible mediators of reduced grade 2-3 BPD with darbepoetin

Reduction in RBC transfusions

Darbepoetin reduced the number of RBC transfusions

- Mean transfusion number: 1.9 (2.8) vs. 3.3 (3.6)
- Ever transfused: 54% vs 76%

Higher transfusion volume associated with greater BPD risk

Transfusions linked to acute lung injury in older patients

Higher RBC mass (circulating erythrocyte volume)

Darbepoetin increased RBC mass

- Mean RBC mass at 42 days: 44mL vs 37mL

Higher RBC mass may improve oxygen delivery

Hematologic measures and risk of grade 2-3 BPD

Exposure	Grade 2-3 BPD	No BPD Grade 1	Adjusted mean diff or RR (95% CI) †
Number of RBC transfusions, mean (SD)	4.3 (3.9)	1.5 (2.2)	1.11 (1.08 to 1.14)
RBC mass at 42 days*, mL - mean (SD)	38.3 (9.3)	44.1 (11.8)	0.97 (0.95 to 0.99)

* Calculated as patient weight × hematocrit × blood volume (assumed constant)
† GEE models adjusted for GA stratum, center, and familial clustering

Results: Mediation analysis

Grade 2-3 BPD among survivors to 36 weeks' PMA

Mediator	Darbe direct effect RR (95% CI)*	Mediator indirect effect RR (95% CI)*	Percent mediated
No. of RBC transfusions	0.93 (0.58-1.27)	0.75 (0.61-0.88)	76%
RBC mass at 42 days	0.88 (0.70-1.06)	0.73 (0.62-0.84)	67%

Death or grade 2-3 BPD at 36 weeks' PMA

No. of RBC transfusions	0.98 (0.74-1.23)	0.84 (0.73-0.95)	90%

* GLM models with binomial distribution and log link, adjusted for GA stratum and study center. 95% CI by bootsrapping (n=1000)

Which matters most: RBC transfusions vs. RBC mass?

Model covariate	Adjusted RR (95% CI)* for grade 2-3 BPD among survivors to 36 weeks'	P-value
Darbepoetin	0.98 (0.74-1.32)	0.91
No. of RBC transfusions	1.10 (1.06-1.14)	<0.001
RBC mass at 42d of age	0.98 (0.96-1.001)	0.06

Only the number of RBC transfusions was independently associated with grade 2-3 BPD when Darbe treatment group and RBC mass were simultaneously included in a regression model

* Poisson regression adjusted for the listed covariates plus GA stratum and study center.

Darbe vs PENUT Trials - Transfusion rate and BPD

	Never transfused RBCs			BPD treatment vs placebo
Trial	Darbe/Epo	Placebo	Diff	
Darbe	46%	24%	22%	Grade 2-3 BPD: 35% vs 46% RR 0.78 (0.64 - 0.96)
PENUT[1]	28%	13%	15%	Severe BPD: 36% vs 35% RR: 1.07 (0.91-1.26)

[1] Juul SE et al. N Engl J Med. 2020

Conclusions

- Darbepoetin administered through 35 weeks' PMA reduced:
  - Grade 2-3 BPD among survivors to 36 weeks' PMA
  - Death or grade 2-3 BPD at 36 weeks' PMA
  - Duration of supplemental respiratory support and oxygen therapy through 120 days

- Darbepoetin did not affect the risk of the evaluated post-discharge respiratory outcomes.

Conclusions

- The BPD result observed in this trial differs from other recent erythropoietic and high vs. low transfusion trials.
- It is uncertain whether this difference is due to chance or a true beneficial treatment effect from darbepoetin.
- Reduction in RBC transfusions may have contributed to the observed decrease in BPD risk with darbepoetin.
- Strategies that safely eliminate the need for RBC transfusions should continue to be investigated as potential means to improve outcomes in extremely preterm infants.

Neonatal Research Network Centers (2016-2021)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- University of Utah

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