NICHD

NEONATAL RESEARCH NETWORK

Heterogeneity in the Effect of Hydrocortisone in Infants Enrolled in the NICHD NRN Hydrocortisone Trial

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Disclosures

- Speaker: Samuel Gentle

- Dr. Gentle 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 the discussion of investigational use for hydrocortisone therapy.

Introduction

- Few pharmacotherapies reduce the risk for bronchopulmonary dysplasia (BPD) in extremely preterm infants.
- The NICHD NRN Hydrocortisone Trial compared hydrocortisone to placebo in extremely preterm infants on mechanical ventilation from postnatal d14-28.
- Hydrocortisone treatment did not improve survival without BPD.
- The effect of hydrocortisone treatment may be affected by baseline risk for BPD.

Watterberg et al. *NEJM.* 2022.

Introduction: Heterogeneity of Treatment Effect

- The average treatment effect from a RCT assumes homogeneity across the included patient population.
- Analyzing a RCT for heterogeneity of treatment effect may identify subgroups with greater benefit or harm.
- Subgroup analyses within RCTs typically use a single characteristic.
- By using a risk score that accounts for multiple characteristics, outcomes can be compared across different distributions of risk.

	Patient 1	**Patient 2**
Gestational age	29	25
Birth weight	1249	600
Sex	Female	Male
FiO_2	0.30	0.60
Risk for Moderate to Severe BPD or Death*	33%	84%

*Laughon et al. *AJRCCM.* 2011.
Kent et al. *Ann Intern Med.* PMID: 31711134. 2020.

Hypothesis

P. In preterm infants <30 weeks' gestation on mechanical ventilation for at least 7 days and between 14-28 postnatal days of age,

I. Baseline risk for grade 2-3 BPD or death will modify the effect of 10 days of hydrocortisone therapy (cumulative 18 mg/kg)

C. Compared to placebo

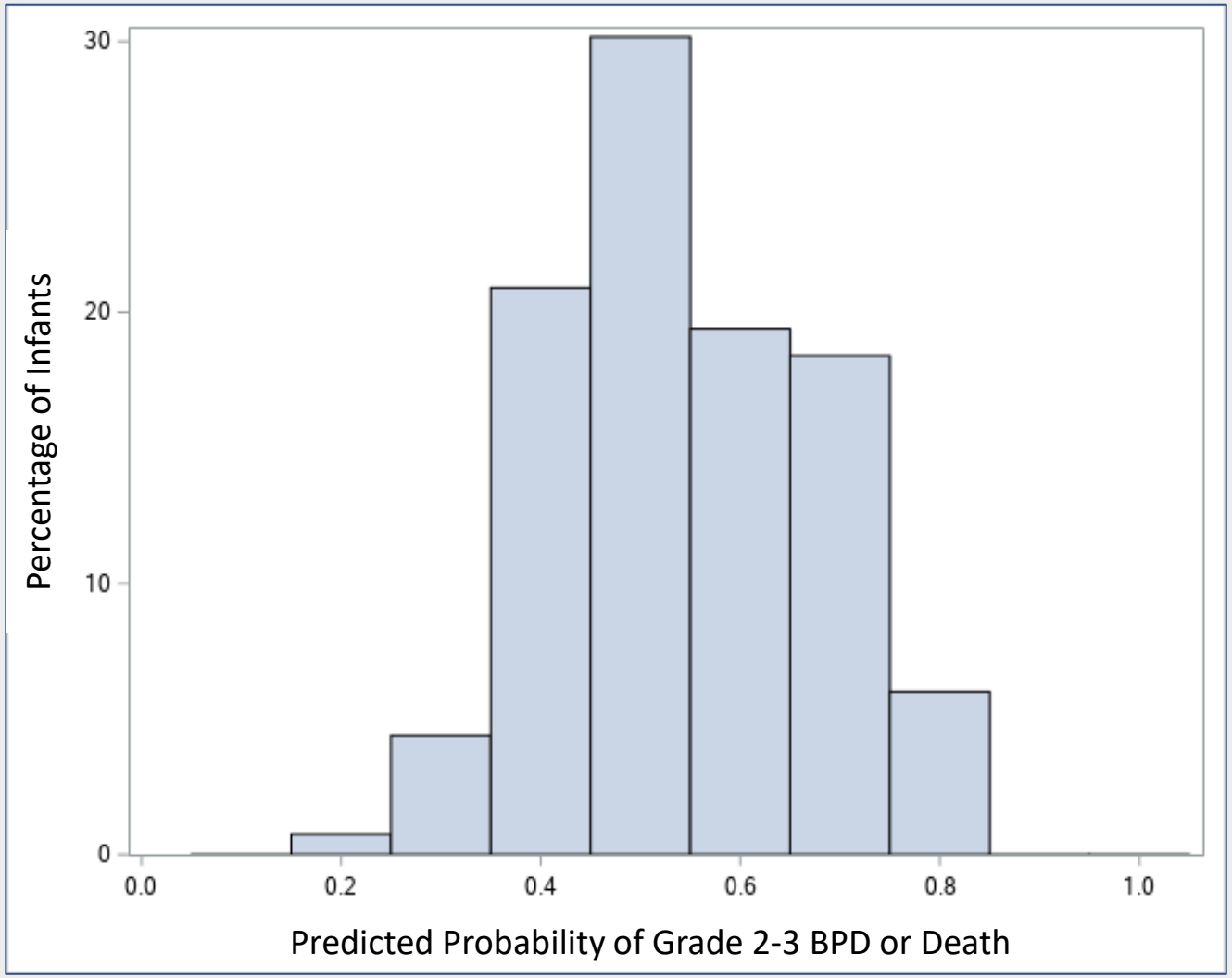
O. Efficacy: Grade 2-3 BPD or death

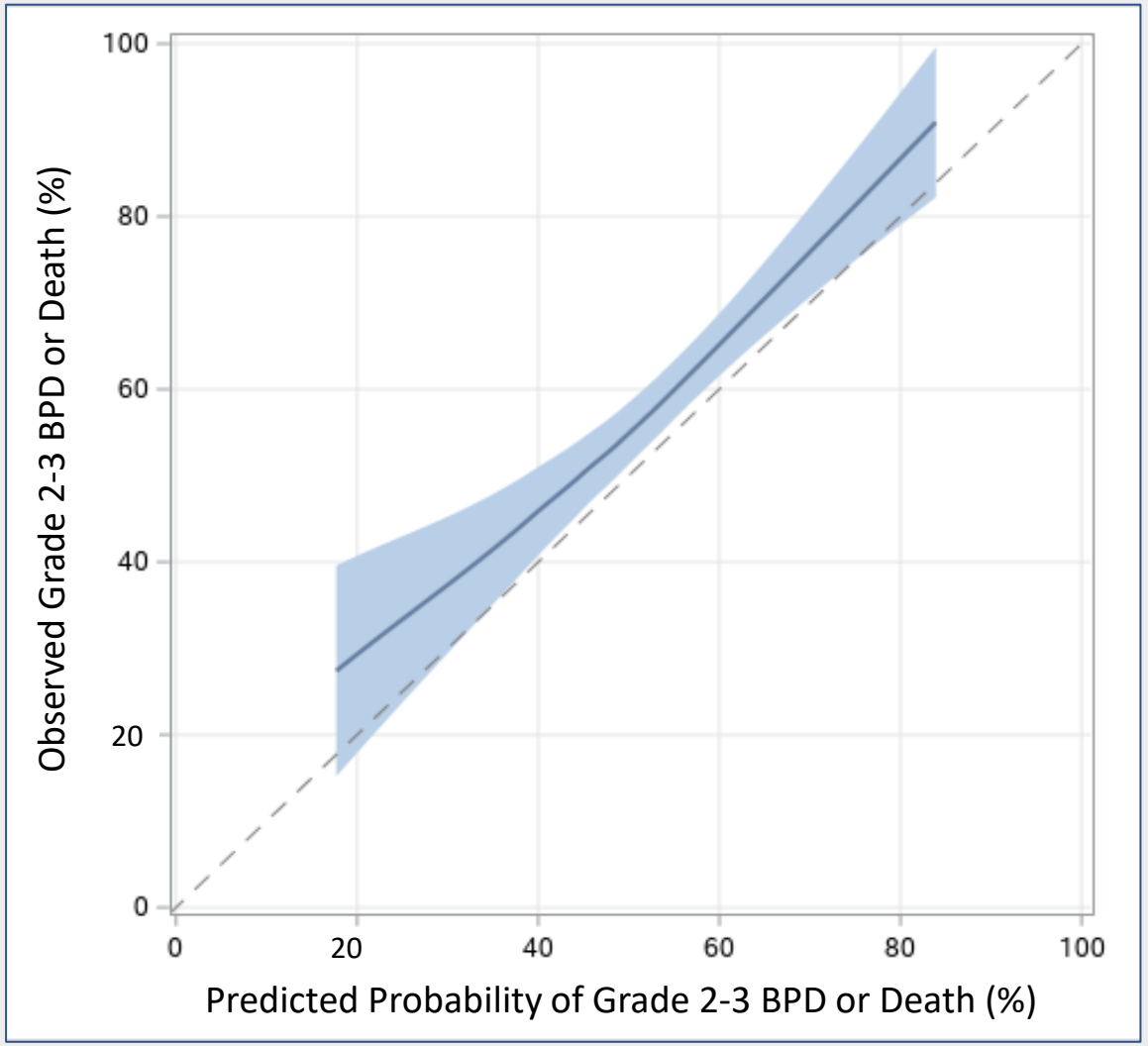
Safety: Moderate or severe neurodevelopmental impairment (NDI) or death

Methods

- Secondary analysis of the NICHD NRN Hydrocortisone Trial
- NRN BPD Risk Estimator used to estimate baseline risk of grade 2-3 BPD or death at postnatal day 14
- Primary analysis: tested for an interaction between treatment group and baseline risk as a continuous variable
- Infants further stratified into quartiles of baseline risk for grade 2-3 BPD or death
- Secondary analysis examined the interaction between treatment group and open label dexamethasone use

Results: Baseline Risk and Calibration





Results: Baseline Demographics

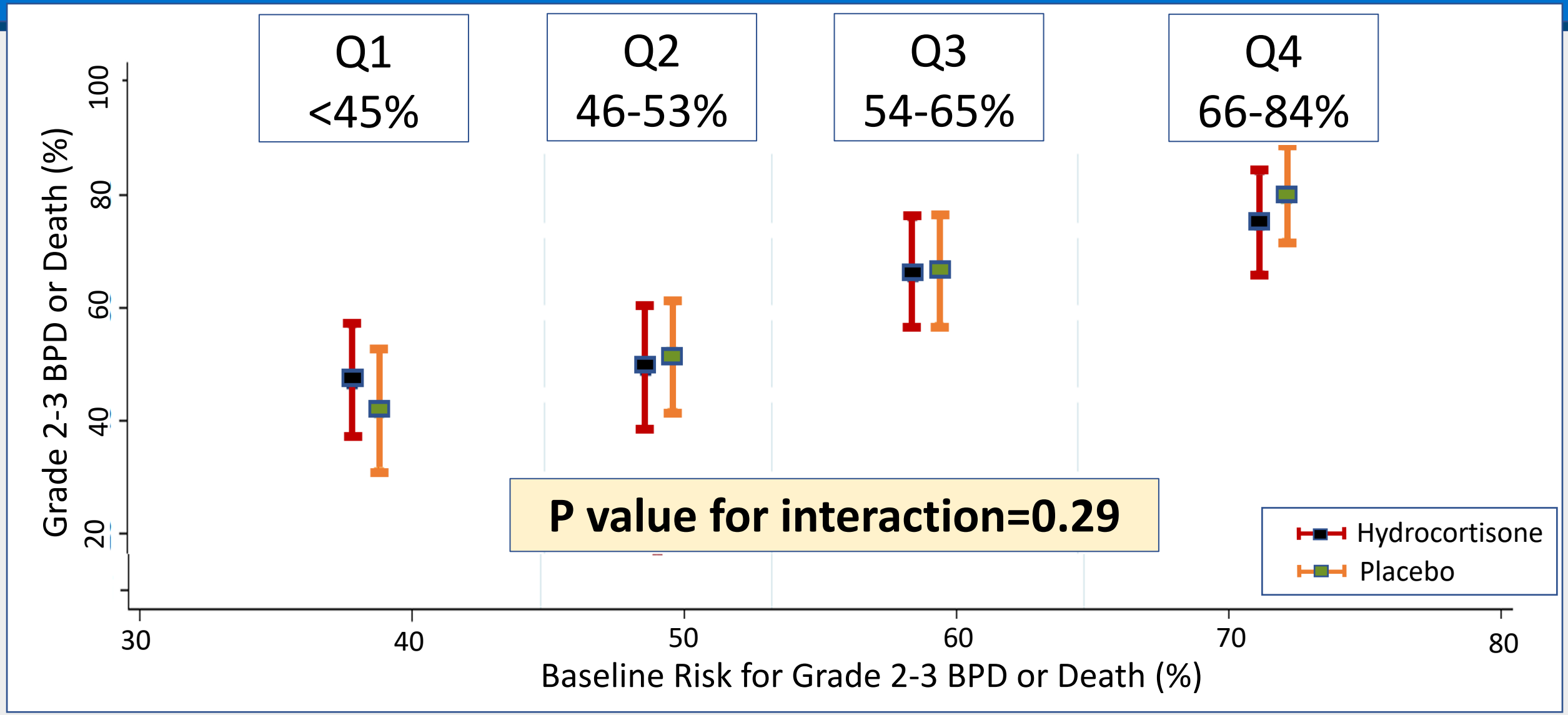
	Quartile 1 <45%		Quartile 2 46-53%		Quartile 3 54-65%		Quartile 4 66-84%	
	HC	Placebo	HC	Placebo	HC	Placebo	HC	Placebo
	n=110	n=89	n=89	n=111	n=99	n=101	n=100	n=100
Gestational age (wks), median	25	25	25	25	24	25	25	25
Birth weight (g), median	773	848	700	730	665	670	633	630
Male: %	24	36	53	65	56	65	58	65
Nonwhite race: %	40	43	52	47	38	50	33	50

Results: Selected Clinical Characteristics

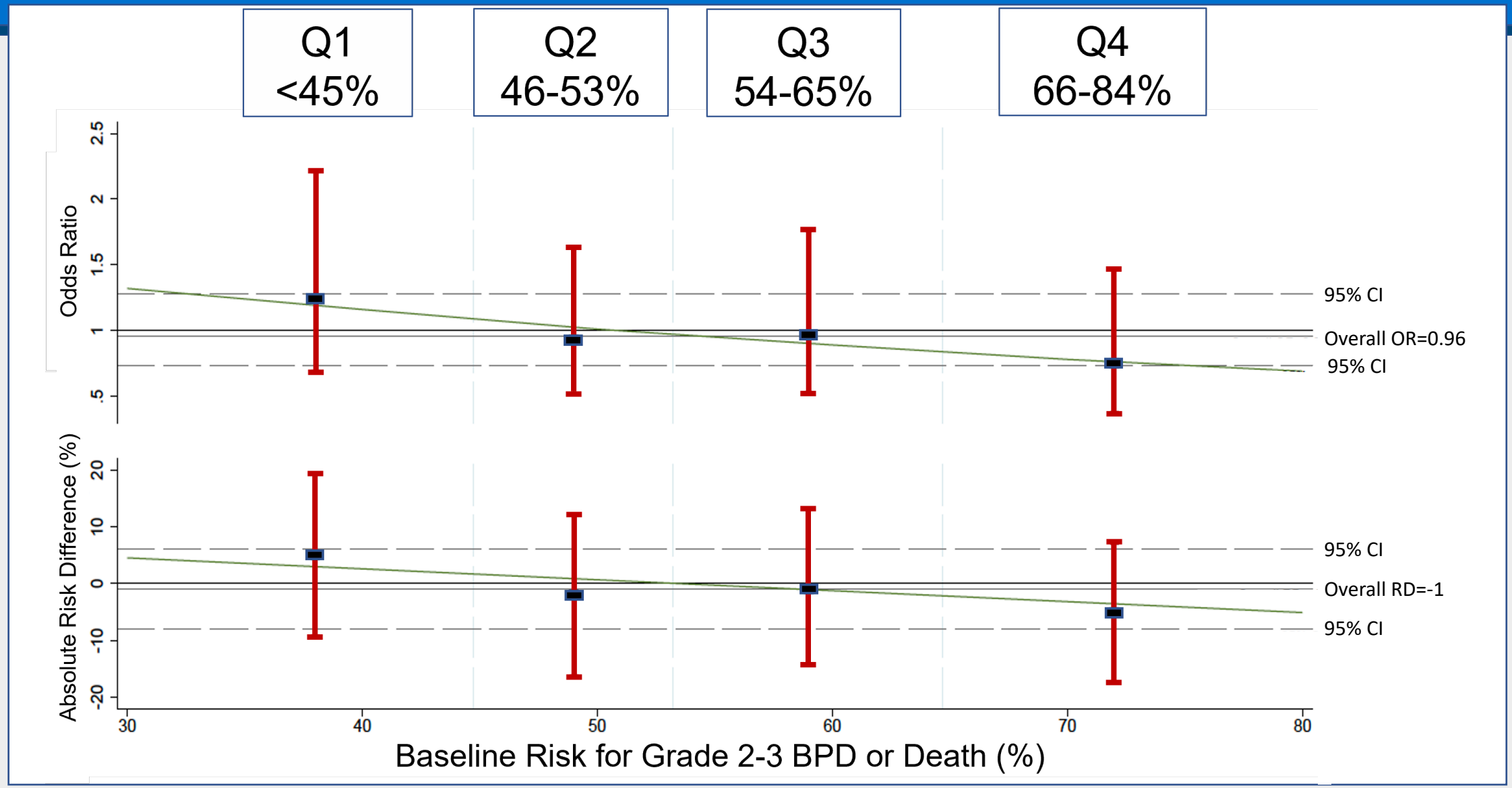
	Quartile 1 <45%		Quartile 2 46-53%		Quartile 3 54-65%		Quartile 4 66-84%	
	HC	Placebo	HC	Placebo	HC	Placebo	HC	Placebo
	n=110	n=89	n=89	n=111	n=99	n=101	n=100	n=100
Days of mechanical ventilation*: median	33	29	36	37	40	44.5	43	50
Highest FiO2 on Day 14: median	36	35	46	38	48	48	60	60
Highest FiO2 at enrollment: median	33	33	45	39	51	50	73	70
Extubation failure*: %	10	6	15	14	14	16	23	19
Open label dexamethasone exposure: %	32	24	31	34	47	56	51	55

*among surviving infants by 36wks PMA

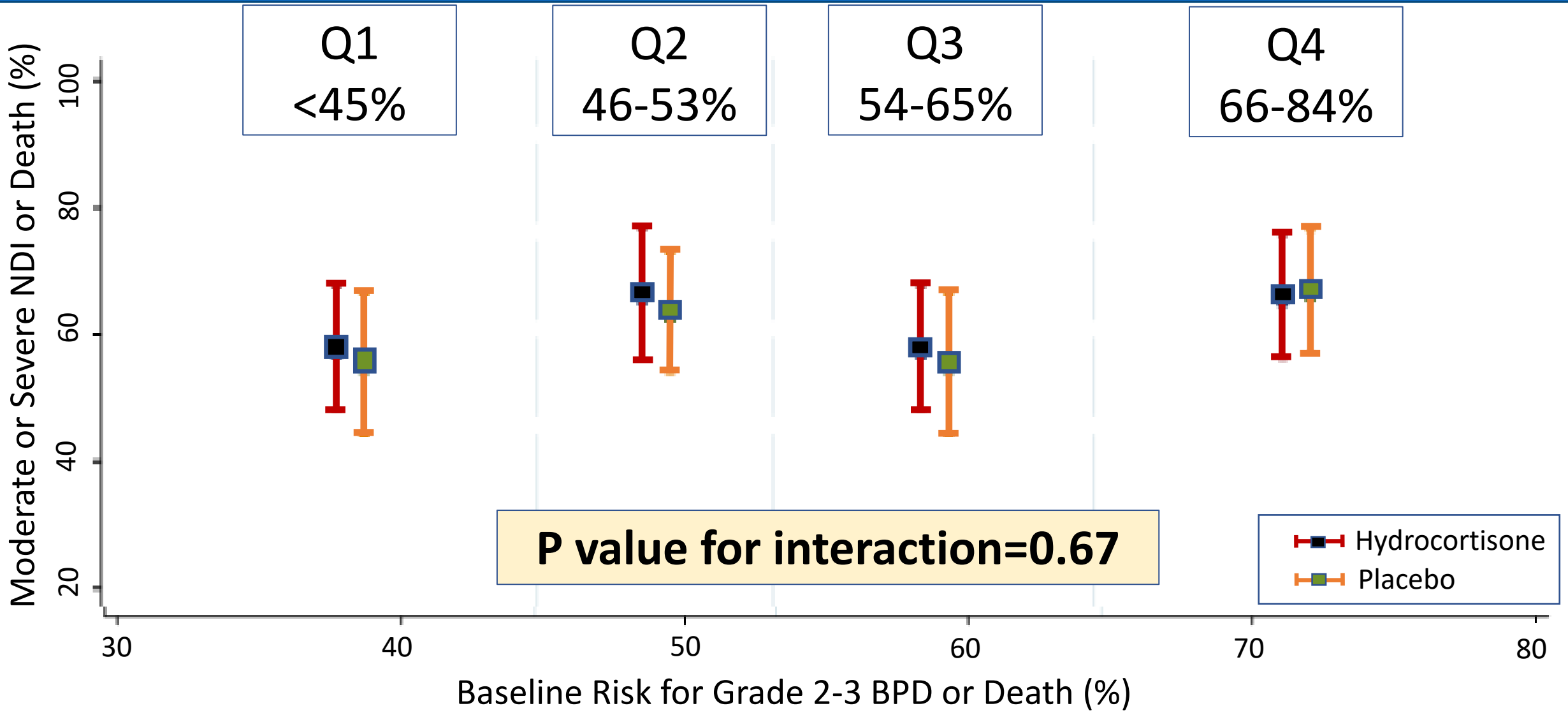
Results: Grade 2-3 BPD or Death



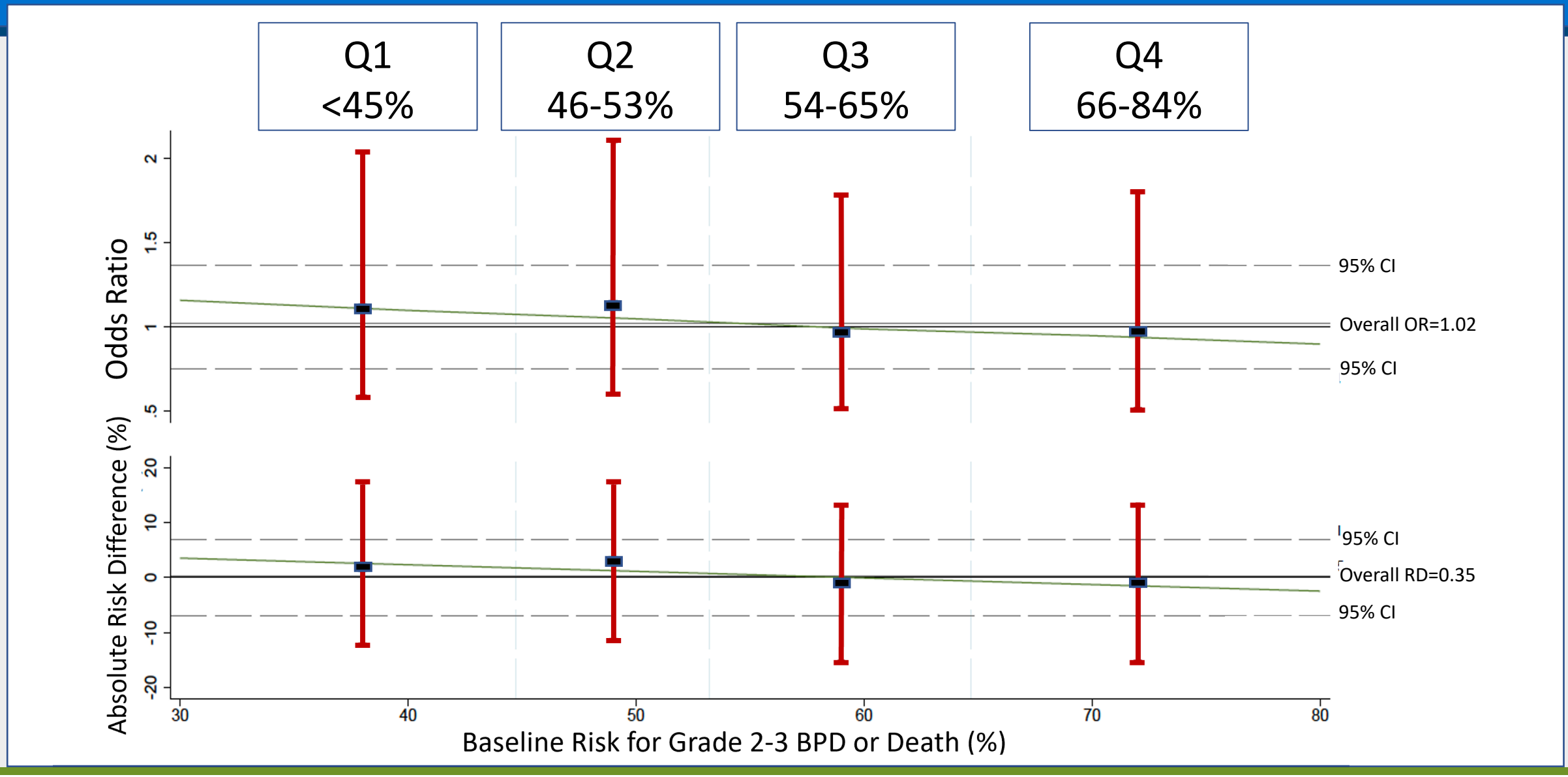
Results: Grade 2-3 BPD or Death



Results: Moderate or Severe NDI or Death



Results: Moderate or Severe NDI or Death



Results: Open Label Dexamethasone

- Use of open-label dexamethasone occurred in 38% of hydrocortisone-exposed and 39% of placebo-exposed infants
- No significant interaction between dexamethasone exposure and grade 2-3 BPD or death (p=0.21)
- No significant interaction between dexamethasone exposure and moderate or severe neurodevelopmental impairment or death (p=0.75)

Conclusions

- There is no clear difference in the effect of hydrocortisone on **death/BPD** or **death/NDI** by baseline risk.
- In the trial population, hydrocortisone therapy does not reduce **death/BPD** or **death/NDI** when considering all or subgroups of infants.
- Open-label dexamethasone use did not modify the effect of hydrocortisone on death/BPD or death/NDI.
- Additional secondary analyses for heterogeneity of treatment effect should be considered in previous trials of hydrocortisone therapy.

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