Supplementary Online Content

Onland W, Cools F, Kroon A, et al; STOP-BPD Study Group. Effect of hydrocortisone therapy initiated 7 to 14 days after birth on mortality or bronchopulmonary dysplasia among very preterm infants receiving mechanical ventilation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.21443

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Reported causes of death

	No./Total (%)	
	Hydrocortisone	**Placebo**
Pulmonary deterioration	13/28 (46.4)	16/45 (35.6)
Sepsis	7/28 (25.0)	12/45 (26.7)
Necrotizing enterocolitis	4/28 (14.3)	9/45 (20.0)
Cerebral hemorrhage	3/28 (10.7)	4/45 (8.9)
Persistent pulmonary hypertension	1/28 (3.6)	0/45 (0.0)
Other causes	0/28 (0.0)	4/45 (8.9)

eTable 2: SUSARs, and SAEs and protocol deviations reported until discharge home

	No./Total No. (%)		
	Hydrocortisone	**Placebo**	**Crude Absolute Risk reduction %, (95%CI)**
SUSARs	none	none	-
SAEs[a]			
Patients with at least one SAE	9/181 (5.0)	13/190 (6.8)	-2.0 (-7.0 to 3.0)
Total number of SAEs reported	11	15	
Circulatory/cardiac	2	2	
Gastrointestinal/surgical	2	6	
Hematology	2	1	
Renal/electrolyte disturbances	1	2	
ENT complications[b]	3	1	
Other complications	1	1	
Protocol deviations			
Open label not according to study protocol	6	22	
Study medication error	2	1	
Unblinding	-	3	

CI denotes confidence interval; SUSAR denotes suspected unexpected serious adverse drug reactions; SAE denotes serious adverse events.

[a] Participants could have more than one SAE.

[b] ENT ear nose throat

eTable 3: Pre-specified sensitivity analyses[1] of the primary composite outcome death or bronchopulmonary dysplasia at 36 weeks postmenstrual age

Analysis	**No./Total (%)**			
	Hydrocortisone	**Placebo**	**Adjusted Odds ratio (95% CI)**	**P-value**
Multivariable logistic regression model including treatment and preselected baseline risk factors[a]	128/181 (70.7)	140/190 (73.7)	0.84 (0.53 to 1.34)	.47
Generalized estimating equations model to account for clustering of outcomes within multiple births including treatment and the randomization stratification factors	128/181 (70.7)	140/190 (73.7)	0.86 (0.53 to 1.40)	.55
Alternative definition of bronchopulmonary dysplasia[b], logistic regression model including treatment and the randomization stratification factors	119/181 (65.7)	133/190 (70.0)	0.82 (0.53 to 1.28)	.38
Per-protocol population[c]	122/173 (70.5)	119/162 (73.5)	0.86 (0.53 to 1.40)	.55
As-treated population[d]	213/288 (74.0)	52/80 (65.0)	1.54 (0.89 to 2.67)	.12

CI denotes confidence interval.

[a] Preselected baseline risk factors for bronchopulmonary dysplasia: gestational age (<, ≥27 weeks), chorioamnionitis (yes, no), respiratory index at randomization (≤, > median), gender (male, female), and multiple birth (yes, no).

[b] Infants on CPAP and HFNC in room air classified as having mild BPD.

[c] Only infants treated according to the study protocol analyzed (see eFigure 1). Summary baseline characteristics of the per protocol hydrocortisone and placebo treatment groups were similar to those of the respective intention to treat treatment groups with no clinical differences between PP comparison.

[d] Infants analyzed based on actual treatment received (see eFigure 1). Analysis confounded by indication; baseline prognostic balance generated by the original random treatment allocation is lost due to substantial cross-over of placebo treated infants with open label corticosteroids to the as treated analysis hydrocortisone group, leaving a small selected as treated analysis placebo group.

eTable 4: Pre-specified exploratory subgroup analyses of the primary composite outcome death or bronchopulmonary dysplasia at 36 weeks postmenstrual age in the intention-to-treat population

	No./Total (%)			
	Hydrocortisone	**Placebo**	**Crude Relative risk (95% CI)**	**P-value for interaction test[a]**
Total population	128/181 (70.7)	140/190 (73.7)	0.96 (0.85 to 1.09)	N.A.
Subgroups				
Gestational age < 27 weeks	106/149 (71.1)	119/159 (74.8)	0.95 (0.83 to 1.09)	.70
Gestational age ≥ 27 weeks	22/32 (68.8)	21/31 (67.7)	1.01 (0.72 to 1.42)	
Chorioamnionitis	33/50 (66.0)	38/53 (71.7)	0.92 (0.71 to 1.20)	.76
No chorioamnionitis	95/131 (72.5)	102/137 (74.5)	0.97 (0.84 to 1.13)	
Respiratory index ≤ median	54/77 (70.1)	73/104 (70.2)	1.00 (0.82 to 1.21)	.45
Respiratory index > median	74/104 (71.2)	67/86 (77.9)	0.91 (0.77 to 1.08)	
Male	66/95 (69.5)	82/109 (75.2)	0.92 (078. to 1.10)	.50
Female	62/86 (72.1)	58/81 (71.6)	1.01 (0.83 to 1.22)	
Multiple birth	50/70 (71.4)	40/54 (74.1)	0.96 (0.78 to 1.20)	.96
Singleton	78/111 (70.3)	100/136 (73.5)	0.96 (0.82 to 1.12)	
Centers administering hydrocortisone prior to study	54/75 (72.0)	55/78 (70.5)	1.02 (0.84 to 1.25)	.42
Centers administering dexamethasone prior to study	74/106 (69.8)	85/112 (75.9)	0.92 (0.78 to 1.08)	

CI denotes confidence interval; N.A. denotes not applicable.

[a] Subgroup analyses were performed and statistically tested for the primary composite outcome with interaction effects of the specific subgroup and treatment in logistic regression models. Statistical tests for interaction directly examine the strength of evidence for the treatment effect varying between subgroups.[2-4] Together with the statistical tests of the treatment-by-subgroup interaction terms, treatment effect estimates within each specific subgroup category are estimated with their corresponding 95% confidence intervals[5], independent of whether the test of the specific interaction term is statistically significant. With the exception of the subgroup gestational age, being a randomization stratification factor, interpretation of the other subgroups is hampered by potential confounder disbalance.

eTable 5: Post hoc[a] sensitivity analyses for death at 36 weeks postmenstrual age

	No./Total No. (%)			
	Hydrocortisone	**Placebo**	**Odds ratio (95% CI)**	**P-value**
Multivariable logistic regression model including treatment, postulated risk factors associated with death[b]	28/181 (15.5)	45/190 (23.7)	Adjusted OR: 0.56 (0.32 to 0.96)	.03
Per-protocol population	26/173 (15.0)	39/162 (24.1)	Crude OR 0.56 (0.32 to 0.97)	.04

CI denotes confidence interval.

[a] To allow more insight in the observed differential death rates at 36 weeks postmenstrual age between both treatment groups, we carefully assessed the plausibility of this finding using these post hoc sensitivity analyses.[5,6]

[b] Risk factors: gestational age (<, ≥27 weeks), small for gestational age, respiratory index at randomization (≤, > median), gender (male/female), and multiple birth (yes/no)

eTable 6: Post hoc exploratory subgroup analyses[a] of death at 36 weeks postmenstrual age for postulated risk factors associated with death in the intention-to-treat population

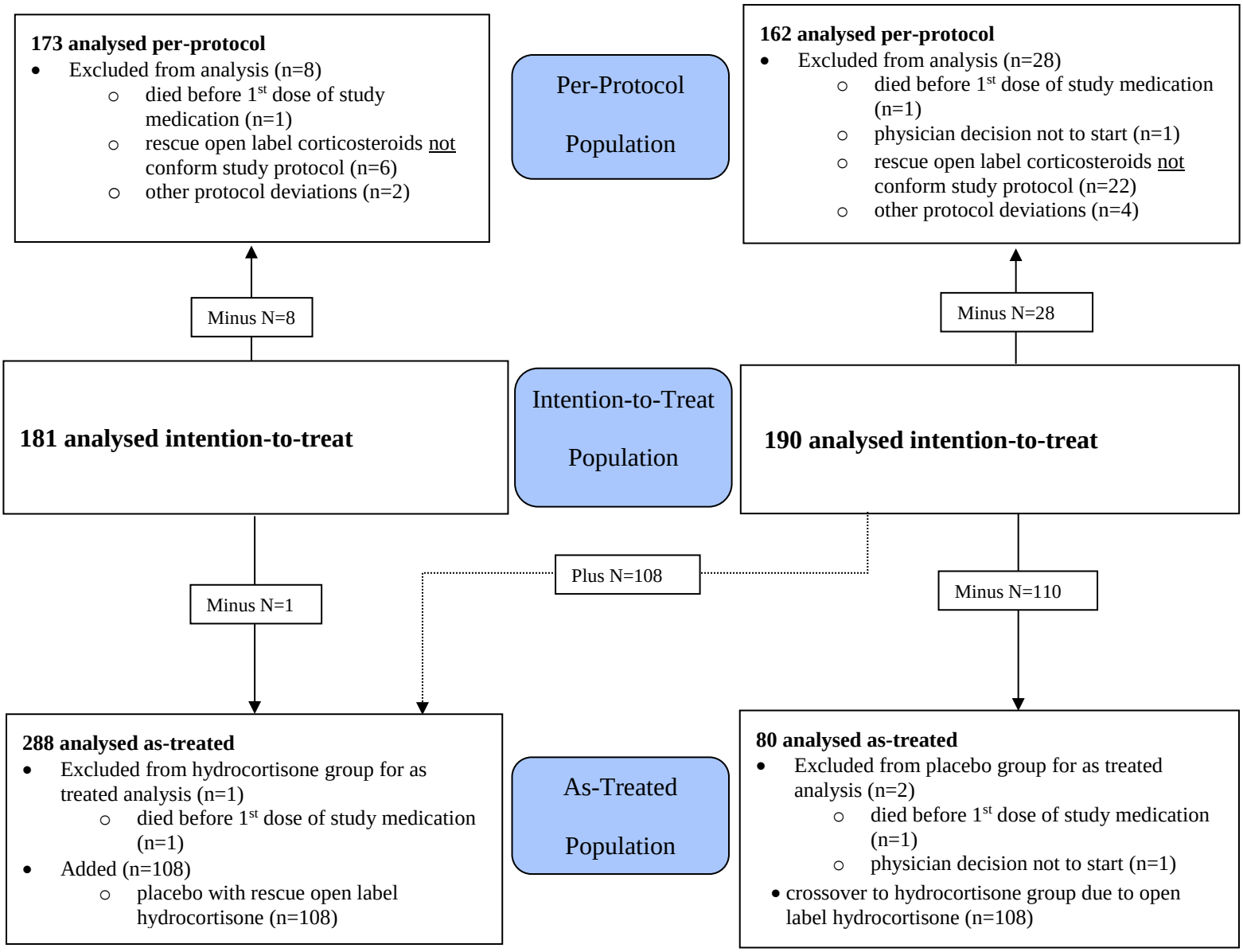
	No./Total No. (%)			
	Hydrocortisone	**Placebo**	**Crude Relative risk (95% CI)**	**P-value for interaction test[b]**
Total population	28/181 (15.5)	45/190 (23.7)	0.65 (0.43 to 0.9997)	N.A.
Subgroup				
Gestational age < 27 weeks	21/149 (14.1)	42/159 (26.4)	0.53 (0.33 to 0.86)	.03
Gestational age ≥ 27 weeks	7/32 (21.9)	3/31 (9.7)	2.48 (0.70 to 8.77)	
Small for gestational age yes	6/26 (23.1)	13/38 (34.2)	0.68 (0.29 to 1.55)	.91
Small for gestational age no	22/155 (14.2)	32/152 (21.1)	0.67 (0.41 to 1.11)	
Respiratory index at randomization ≤ median	6/77 (7.8)	24/104 (23.1)	0.34 (0.15 to 0.79)	.07
Respiratory index at randomization > median	22/104 (21.2)	21/86 (24.4)	0.87 (0.51 to 1.47)	
Male gender	16/95 (16.8)	25/109 (22.9)	0.73 (0.42 to 1.29)	.55
Female gender	12/86 (14.0)	20/81 (24.7)	0.57 (0.30 to 1.08)	
Multiple birth	11/70 (15.7)	15/54 (27.8)	0.57 (0.28 to 1.13)	.62
Singleton	17/111 (15.3)	30/136 (22.1)	0.69 (0.41 to 1.19)	

CI denotes confidence interval; N.A. denotes not applicable.

[a] To allow more insight in the observed differential death rates at 36 weeks postmenstrual age, we carefully assessed the plausibility of this finding using these post hoc subgroup analyses.[5,6]

[b] Subgroup analyses were performed and statistically tested for the outcome death at 36 weeks postmenstrual age with interaction effects of the specific subgroup and treatment in logistic regression models. Statistical tests for interaction directly examine the strength of evidence for the treatment effect varying between subgroups.[2-4] Together with the statistical tests of the treatment-by-subgroup interaction terms, we will report treatment effect estimates within each specific subgroup category with their corresponding 95% confidence interval[5], independent of whether the test of the specific interaction term is statistically significant. With the exception of the subgroup gestational age, being a randomization stratification factor, interpretation of the other subgroups is hampered by potential confounder disbalance.

eFigure. Supplemental flow of infants for the per-protocol and as-treated analysis populations



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