ORIGINAL ARTICLE

Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus

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ABSTRACT

BACKGROUND

Cyclooxygenase inhibitors are commonly used in infants with patent ductus arteriosus (PDA), but the benefit of these drugs is uncertain.

METHODS

In this multicenter, noninferiority trial, we randomly assigned infants with echocardiographically confirmed PDA (diameter, >1.5 mm, with left-to-right shunting) who were extremely preterm (<28 weeks' gestational age) to receive either expectant management or early ibuprofen treatment. The composite primary outcome included necrotizing enterocolitis (Bell's stage IIa or higher), moderate to severe bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age. The noninferiority of expectant management as compared with early ibuprofen treatment was defined as an absolute risk difference with an upper boundary of the one-sided 95% confidence interval of less than 10 percentage points.

RESULTS

A total of 273 infants underwent randomization. The median gestational age was 26 weeks, and the median birth weight was 845 g. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 (63.5%) in the early-ibuprofen group (absolute risk difference, –17.2 percentage points; upper boundary of the one-sided 95% confidence interval [CI], –7.4; P<0.001 for noninferiority). Necrotizing enterocolitis occurred in 24 of 136 infants (17.6%) in the expectant-management group and in 21 of 137 (15.3%) in the early-ibuprofen group (absolute risk difference, 2.3 percentage points; two-sided 95% CI, –6.5 to 11.1); bronchopulmonary dysplasia occurred in 39 of 117 infants (33.3%) and in 57 of 112 (50.9%), respectively (absolute risk difference, –17.6 percentage points; two-sided 95% CI, –30.2 to –5.0). Death occurred in 19 of 136 infants (14.0%) and in 25 of 137 (18.2%), respectively (absolute risk difference, –4.3 percentage points; two-sided 95% CI, –13.0 to 4.4). Rates of other adverse outcomes were similar in the two groups.

CONCLUSIONS

Expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age. (Funded by the Netherlands Organization for Health Research and Development and the Belgian Health Care Knowledge Center; BeNeDuctus ClinicalTrials.gov number, NCT02884219; EudraCT number, 2017-001376-28.)

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Patent ductus arteriosus (PDA) is common in preterm infants,[1] and its management is a subject of debate.[2-5] This condition, which occurs when the vessel connecting the aorta and the pulmonary artery does not close normally, is associated with increased neonatal mortality and morbidity, including bronchopulmonary dysplasia,[6] necrotizing enterocolitis,[7] and intraventricular hemorrhage.[8]

Meta-analyses of randomized, controlled trials showed that pharmacologic treatment with cyclooxygenase inhibitors induced PDA closure but had no beneficial effect on clinical outcomes.[9,10] The lack of evidence supporting a causal relationship between PDA and neonatal morbidity and mortality and the potential adverse effects of pharmacologic treatment have led to more frequent expectant (i.e., nonintervening) management of PDA.[11] However, the evidence to support this strategy is limited and contradictory.[12]

We performed the Early Treatment Versus Expectative Management of PDA in Preterm Infants (BeNeDuctus) trial in extremely preterm infants with echocardiographically confirmed PDA to assess whether expectant management would be noninferior to early ibuprofen treatment with respect to necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a postmenstrual age of 36 weeks.

Methods

Trial Design

The trial was an international, multicenter, randomized, controlled noninferiority trial conducted at 17 neonatal intensive care units in the Netherlands, Belgium, and Denmark and was funded by the Netherlands Organization for Health Research and Development and the Belgian Health Care Knowledge Center. Approval was granted by the ethics committees at Radboud University, Cliniques Universitaires de Bruxelles–Hôpital Erasme, and the Central Denmark Region.

The trial protocol and statistical analysis plan have been published previously[13,14] and are available in the protocol document with the full text of this article, available at NEJM.org. Written informed consent was obtained from the parents or guardians of all the infants who were included in the trial.

Patients

Infants with extremely premature birth (gestational age, <28 weeks) who had echocardiographically confirmed PDA with a diameter of more than 1.5 mm at the smallest point and who had a transductal left-to-right shunt between 24 and 72 hours postnatal age were eligible.[13] Exclusion criteria were contraindications to the administration of ibuprofen, the use of a cyclooxygenase inhibitor before randomization, persistent pulmonary hypertension (defined as a transductal right-to-left shunt during ≥33% of the cardiac cycle), a congenital heart defect (other than PDA or patent foramen ovale), a life-threatening congenital defect or chromosomal abnormality, or a congenital anomaly that was associated with an abnormal neurodevelopmental outcome.[13]

Randomization

As part of the consent process, parents were informed of the uncertainty as to whether PDA plays a causal role in neonatal morbidity and mortality or whether the condition is simply a marker of immaturity and that the best approach to management thus remains unclear. After provision of consent, the infants were randomly assigned to receive either expectant management or early ibuprofen treatment. Randomization was coordinated centrally with the use of a Web-based system and was stratified according to trial center and gestational age (<26 weeks or ≥26 weeks). Block sizes varied within a range of 4 to 8. Multiple-birth infants underwent independent randomization, unless the parents explicitly requested that all siblings be enrolled in the same trial group.

Intervention

In the expectant-management group, no treatment was initiated with the intention of closing the PDA. Unblinded echocardiography was allowed if indicated by the local pediatric cardiologist or after a primary-outcome event had occurred by a postmenstrual age of 36 weeks. Open-label pharmacologic treatment could be considered only if prespecified criteria had been met for clinical and echocardiographic findings of cardiovascular failure associated with a clinically significant left-to-right shunt (Table S1A in the Supplementary Appendix, available at NEJM.org).[13]

In the early-ibuprofen group, ibuprofen was administered according to the local protocol, preferably within 3 hours after randomization. After a complete course of ibuprofen, echocardiographic evaluation was performed at least 12 hours after the last dose. Closure was defined as a ductus arteriosus that either could not be visualized with the use of color Doppler imaging or had a transductal diameter of less than 0.5 mm.[13] If closure had not been achieved, a second course of ibuprofen was given. After two failed courses, a third course of ibuprofen or ductal ligation could be considered if prespecified criteria had been met for clinical and echocardiographic findings of cardiovascular failure associated with a clinically significant left-to-right shunt (Table S1B).[13]

OUTCOMES

The primary outcome was a composite of necrotizing enterocolitis (defined as Bell's stage IIa or higher),[15] moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a postmenstrual age of 36 weeks. In accordance with the international standard criteria of Bancalari and Claure,[16] bronchopulmonary dysplasia was defined as the need for supplemental oxygen or positive-pressure ventilatory support at a postmenstrual age of 36 weeks after at least 28 cumulative days of supplemental oxygen. This diagnosis included the performance of an oxygen reduction test according to the criteria of Walsh et al.,[17] if indicated (see the Supplementary Methods). If the indicated oxygen reduction test was not performed, a committee of three investigators who had extensive clinical expertise and who were unaware of trial-group assignments assessed the severity of bronchopulmonary dysplasia as mild or moderate. All outcome measures and their definitions are summarized in Table S2.

Information was also collected from the electronic medical record regarding adverse events and serious adverse events that were not among the secondary outcomes, as well as protocol deviations.[14]

STATISTICAL ANALYSIS

For the primary analysis, we defined the noninferiority of expectant management as compared with early ibuprofen treatment as an absolute risk difference with an upper boundary of the one-sided 95% confidence interval of less than 10 percentage points. With an estimated a priori risk for a primary-outcome event of 35%, a type I error of 5%, and a power of 80%, we determined that a sample size of 564 patients (282 per group) would be required to exclude the noninferiority margin. Trial enrollment ended on December 15, 2020, before the anticipated sample size had been reached after the randomization of 273 patients (48.4% of the powered sample size), owing to the discontinuation of funding and slower-than-anticipated recruitment.[14]

We performed both an intention-to-treat analysis that included all the patients who had undergone randomization and a per-protocol analysis that included infants in the expectant-management group who had received open-label pharmacologic treatment after meeting the criteria but that excluded those who did not fulfill the criteria. We also excluded infants in the early-ibuprofen group who had not receive any ibuprofen. We also performed five predefined exploratory subgroup analyses and four sensitivity analyses for the primary outcome. Details regarding these analyses are provided in the Supplementary Methods.

Treatment effects for components of the primary outcome and for secondary dichotomous clinical outcomes are reported as the absolute risk difference and relative risk with two-sided 95% confidence intervals for the expectant-management group as compared with the early-ibuprofen group. No adjustment was made for multiple testing, so the widths of the 95% confidence intervals should not be used in place of hypothesis testing. Normally distributed data are presented as means and standard deviations, and unevenly distributed data are presented as medians with interquartile ranges.

RESULTS

PATIENTS

Between December 2016 and December 2020, a total of 1600 infants who had been born at less than 28 weeks' gestation were admitted to the neonatal intensive care units at the participating centers (Fig. 1). Written informed consent was obtained for 442 infants, of whom 273 (61.8%) underwent randomization (136 to the expectant-management group and 137 to the early-ibuprofen group). The median gestational age was 26.1 weeks

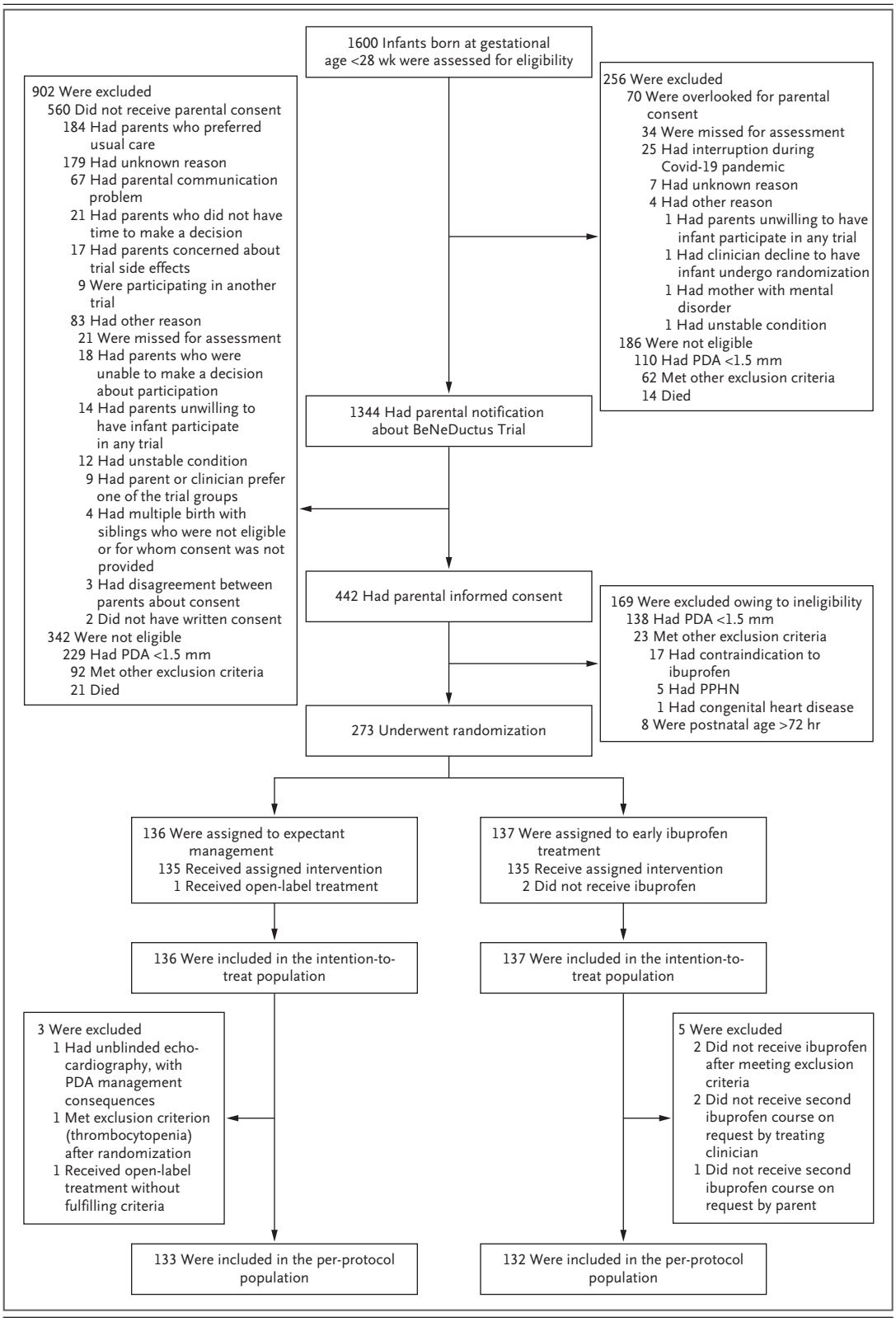

Figure 1 (facing page). Randomization and Outcomes.
At trial sites in which echocardiography was performed as common practice, informed consent could be obtained after echocardiographic assessment of eligibility, whereas at sites in which echocardiography was considered to be a trial procedure, informed consent had to be obtained before eligibility could be assessed. Covid-19 denotes coronavirus disease 2019, PDA patent ductus arteriosus, and PPHN persistent pulmonary hypertension of the newborn.

(interquartile range, 25.1 to 27.0), and the median birth weight was 845 grams (interquartile range, 724 to 980).

In the early-ibuprofen group, ibuprofen was initiated at a median postnatal age of 63 hours (interquartile range, 55 to 70) at a median dose of 10 mg per kilogram of body weight, followed by two subsequent doses of 5 mg per kilogram (Table S3). The baseline characteristics of the infants and their mothers were similar, except for a greater incidence of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) among mothers in the expectant-management group (Table 1 and Table S4). All the infants were included in the intention-to-treat analysis (Fig. S1). The representativeness of the included cohort is shown in Table S5.

PRIMARY OUTCOME

At 36 weeks' postmenstrual age, data regarding the composite primary outcome were available for all 273 infants. In 6 infants, the indicated oxygen reduction test had not been performed, so the severity of bronchopulmonary dysplasia was classified by the committee. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 infants (63.5%) in the early-ibuprofen group (absolute risk difference, –17.2 percentage points; upper boundary of the one-sided 95% confidence interval [CI], –7.4; P<0.001) (Table 2).

SECONDARY OUTCOMES

No material between-group differences in the incidence of necrotizing enterocolitis and death were observed (Table 2). Distributions of reported causes of death were similar in the two groups (Table S6). Moderate-to-severe bronchopulmonary dysplasia was diagnosed in 39 of 117 infants (33.3%) in the expectant-management group and in 57 of 112 infants (50.9%) in the early-ibuprofen treatment group (absolute risk difference, –17.6 percentage points; 95% CI, –30.2 to –5.0). Other secondary outcome measures and cointerventions are shown in Table 3 and Tables S7 and S8.

ADVERSE EVENTS AND PER-PROTOCOL ANALYSIS

The frequencies of adverse events and serious adverse events were similar in the two groups (Table 4).

In the per-protocol analysis, the composite primary outcome was observed in 60 of 133 infants (45.1%) in the expectant-management group and in 83 of 132 (62.9%) in the early-ibuprofen group (absolute risk difference, –17.8 percentage points; upper boundary of the one-sided 95% CI, –7.9; P<0.001) (Table 2). Excluded from the per-protocol analysis were 3 infants in the expectant-management group and 5 infants in the early-ibuprofen group (Fig. 1 and Table S9).

The results of secondary outcomes in the per-protocol analysis were similar to those obtained in the intention-to-treat analysis (Tables S8 and S10).

SUBGROUP ANALYSES

Results for the primary outcome in predefined subgroups are provided in Table S11. The results of subgroup analyses were consistent with the overall findings, with the exception of a potential difference according to sex that suggested a better outcome for expectant management in male infants than in female infants.

SENSITIVITY ANALYSES

In the predefined sensitivity analysis with a modified classification of bronchopulmonary dysplasia,[18] a primary-outcome event was observed in 53 of 136 infants (39.0%) in the expectant-management group and in 68 of 137 infants (49.6%) in the early-ibuprofen group (Table S12).

The adjusted odds ratios after adjustment for multiple births and for the stratification variables of trial center and gestational age were similar to those obtained in the intention-to-treat, per-protocol, and auxiliary sensitivity analyses (Table S12).

Table 1. Maternal and Neonatal Characteristics at Baseline.*

Characteristic	Expectant Management (N=136)	Early Ibuprofen (N=137)
Maternal		
Age — yr	30.4±5.4	31.0±5.1
Race or ethnic group — no. (%)†		
White	102 (75.0)	110 (80.3)
Mediterranean	10 (7.4)	9 (6.6)
African	12 (8.8)	7 (5.1)
Asian	2 (1.5)	4 (2.9)
Latin American	2 (1.5)	3 (2.2)
Unknown	8 (5.9)	4 (2.9)
Obstetrical condition — no. (%)		
Preeclampsia	15 (11.0)	18 (13.1)
HELLP syndrome	7 (5.1)	1 (0.7)
Placental abruption	6 (4.4)	3 (2.2)
PPROM	36 (26.5)	40 (29.2)
Clinical chorioamnionitis	52 (38.2)	53 (38.7)
Medication history — no./total no. (%)		
NSAID	15/136 (11.0)	19/137 (13.9)
Magnesium sulfate	86/136 (63.2)	85/137 (62.0)
Antenatal glucocorticoid		
Any	119/135 (88.1)	126/135 (93.3)
Course completed	73/135 (54.1)	76/135 (56.3)
Tocolysis	79/136 (58.1)	84/135 (62.2)
Type of delivery — no. (%)		
Vaginal	86 (63.2)	76 (55.5)
Cesarean section	50 (36.8)	61 (44.5)
Multiple birth — no. (%)	47 (34.6)	50 (36.5)
Neonatal		
Median gestational age (IQR) — wk	26.1 (25.4–27.0)	26.0 (25.1–27.0)
Median birth weight (IQR) — g	863 (748–984)	825 (715–970)
Outborn — no. (%)	10 (7.4)	8 (5.8)
Male sex — no. (%)	70 (51.5)	70 (51.1)
Median Apgar score at 5 min (IQR)	7 (6–8)	8 (7–8)
Support during fetal–neonatal transition — no. (%)	133 (97.8)	137 (100)
Noninvasive respiratory support	101 (74.3)	103 (75.2)
Invasive respiratory support	32 (23.5)	34 (24.8)
Circulatory support	0	0
Respiratory distress syndrome — no. (%)	117 (86.0)	116 (84.7)
Surfactant administration		
Infants — no./total no. (%)	103/117 (88.0)	106/116 (91.4)
Median no. of surfactant doses (IQR)	1 (1–2)	1 (1–2)
Median postnatal age at time of echocardiography (IQR) — hr	57 (47–65)	57 (44–64)
Median diameter of patent ductus arteriosus (IQR) — mm	2.1 (1.8–2.5)	2.1 (1.8–2.6)

* Plus–minus values are means ±SD. IQR denotes interquartile range; HELLP hemolysis, elevated liver enzymes, and low platelets; NSAID nonsteroidal antiinflammatory drug; and PPROM preterm premature rupture of membranes.
† Race or ethnic group was reported by the mothers.

Table 2. Primary Outcome and Its Components.*

Outcome	Intention-to-Treat Analysis				Per-Protocol Analysis			
	Expectant Management (N=136)	Early Ibuprofen (N=137)	Difference (95% CI)†	Risk Ratio (95% CI)	Expectant Management (N=133)	Early Ibuprofen (N=132)	Difference (95% CI)†	Risk Ratio (95% CI)
	number (percent)		*percentage points*		*number (percent)*		*percentage points*	
Composite primary outcome								
Necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death‡	63 (46.3)	87 (63.5)	−17.2 (−7.4)§	0.73 (0.59 to 0.91)	60 (45.1)	83 (62.9)	−17.8 (−7.9)§	0.72 (0.57 to 0.90)
Components of primary outcome¶								
Necrotizing enterocolitis	24 (17.6)	21 (15.3)	2.3 (−6.5 to 11.1)	1.15 (0.67 to 1.97)	23 (17.3)	21 (15.9)	1.4 (−7.6 to 10.3)	1.09 (0.63 to 1.87)
Moderate-to-severe bronchopulmonary dysplasia‖	39 (33.3)	57 (50.9)	−17.6 (−30.2 to −5.0)	0.66 (0.48 to 0.90)	37 (32.2)	55 (50.5)	−18.3 (−31.0 to −5.6)	0.64 (0.46 to 0.88)
Death	19 (14.0)	25 (18.2)	−4.3 (−13.0 to 4.4)	0.77 (0.44 to 1.32)	18 (13.5)	23 (17.4)	−3.9 (−12.6 to 4.8)	0.78 (0.44 to 1.37)

* CI denotes confidence interval.
† The difference between groups is reported as the absolute risk difference. For the composite primary outcome, the 95% CIs are one-sided. For the components of the primary outcome, the 95% CIs are two-sided.
‡ The primary outcome and its components were measured at 36 weeks' postmenstrual age. Necrotizing enterocolitis was defined as Bell's stage IIa or higher.
§ The value in parentheses is the upper boundary of the one-sided 95% confidence interval; P<0.001 for noninferiority in the prespecified primary analysis.
¶ The 95% confidence intervals for the components of the primary outcome have not been adjusted for multiplicity and should not be used in place of hypothesis testing.
‖ Moderate-to-severe bronchopulmonary dysplasia was measured in 117 infants in the expectant-management group and in 112 in the early-ibuprofen group in the intention-to-treat analysis and in 115 and 109 infants, respectively, in the per-protocol analysis.

DISCUSSION

In this international, randomized, controlled trial, expectant management of PDA in preterm infants was noninferior to early-ibuprofen treatment at a postnatal age of 24 to 72 hours with respect to necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death (the composite primary outcome), as assessed at 36 weeks' postmenstrual age. This observation is in line with previous evidence regarding the lack of beneficial effects of pharmacologic PDA treatment on clinical outcomes reported in meta-analyses[9,10] and in the most recent placebo-controlled, randomized trials investigating various strategies for the management of PDA.[19-22]

A placebo-controlled pilot trial showed that early targeted ibuprofen treatment in preterm infants did not reduce the incidence of bronchopulmonary dysplasia or death.[19] Another study showed that among infants with a mean postnatal age of 8.3 days, nonintervention was noninferior to late ibuprofen treatment with regard to bronchopulmonary dysplasia or death.[20]

In contrast to previous studies with a high incidence of open-label treatment,[19] our trial had a true nonintervention control group, which allowed for a clearer comparison between expectant management and ibuprofen treatment. In another study, investigators did not evaluate any open-label treatment and reported only the results of their per-protocol analysis; in their nonintervention group, judicious fluid restriction, use of diuretics, and changes in ventilatory settings targeting the PDA were allowed.[20]

In our trial, the primary-outcome results suggest harm associated with early ibuprofen exposure, largely driven by a higher incidence of moderate-to-severe bronchopulmonary dysplasia in the early-ibuprofen group than in the expectant-management group. This result contrasts with the general hypothesis that pulmonary hyperperfusion associated with transductal left-to-right shunting is the plausible pathophysiological mechanism for the occurrence of bronchopulmonary dysplasia. According to this hypothesis, PDA closure is expected to normalize pulmonary perfusion, as supported by data from a baboon model showing improved alveolarization after ibuprofen treatment.[23] The suggestion of a higher risk of bronchopulmonary dysplasia in the ibuprofen group is consistent with observational

Table 3. Secondary Outcome Measures (Intention-to-Treat Analysis).*

Secondary Outcome	Expectant Management (N=136)	Early Ibuprofen (N=137)	Difference (95% CI)†	Risk Ratio (95% CI)†
	number (percent)		*percentage points*	
Surgical patent ductus arteriosus ligation	0	3 (2.2)	−2.2 (−4.6 to 0.3)	NA
Death at 28 days	13 (9.6)	25 (18.2)	−8.7 (−16.8 to −0.5)	0.52 (0.28 to 0.98)
Pulmonary hemorrhage	4 (2.9)	1 (0.7)	2.2 (−1.0 to 5.4)	4.03 (0.46 to 35.59)
Pulmonary air leakage	6 (4.4)	16 (11.7)	−7.3 (−13.7 to −0.9)	0.38 (0.15 to 0.94)
Pneumothorax	2 (1.5)	3 (2.2)	−0.7 (−3.9 to 2.5)	0.67 (0.11 to 3.96)
Pulmonary interstitial emphysema	5 (3.7)	13 (9.5)	−5.8 (−11.7 to 0.0)	0.39 (0.14 to 1.06)
Cardiovascular support	60 (44.1)	57 (41.6)	−2.5 (−9.2 to 14.2)	1.06 (0.81 to 1.40)
Volume expansion	45 (33.1)	48 (35.0)	−1.9 (−13.2 to 9.3)	0.94 (0.68 to 1.31)
Inotropes or vasopressors	44 (32.4)	40 (29.2)	−3.2 (−7.8 to 14.1)	1.11 (0.78 to 1.58)
Glucocorticoids	18 (13.2)	15 (10.9)	2.3 (−5.4 to 10.0)	1.21 (0.64 to 2.30)
Renal failure‡	13 (9.6)	13 (9.5)	0.0 (−6.9 to 7.0)	1.01 (0.49 to 2.09)
Intraventricular hemorrhage	51 (37.5)	54 (39.4)	−1.9 (−13.5 to 9.6)	0.95 (0.71 to 1.29)
Grade I or II	40 (29.4)	45 (32.8)	−3.4 (−14.4 to 7.5)	0.90 (0.63 to 1.28)
≥Grade III	11 (8.1)	9 (6.6)	1.5 (−4.7 to 7.7)	1.23 (0.53 to 2.88)
Sepsis	49 (36.0)	60 (43.8)	−7.8 (−19.3 to 3.8)	0.82 (0.61 to 1.10)
Retinopathy of prematurity treatment§	14 (12.2)	12 (10.8)	1.4 (−6.9 to 9.7)	1.13 (0.55 to 2.33)
Cointerventions	86 (63.2)	99 (72.3)	−9.0 (−20.1 to 2.0)	0.88 (0.74 to 1.03)
Glucocorticoids	52 (38.2)	63 (46.0)	−7.8 (−19.4 to 3.9)	0.83 (0.62 to 1.10)
Paracetamol‡	34 (25.0)	52 (38.0)	−13.0 (−23.9 to −2.0)	0.66 (0.46 to 0.95)
Diuretics‡	68 (50.0)	57 (41.6)	8.4 (−3.4 to 20.2)	1.20 (0.93 to 1.56)
	median no. of days (IQR)			**Median Difference (95% CI)¶**
Other support				
Supplemental oxygen	41 (13 to 66)	40 (14 to 69)	—	−1.0 (−9.0 to 6.0)
Respiratory support	55 (34 to 72)	56 (36 to 76)	—	−1.0 (−8.0 to 6.0)
Invasive	4 (0 to 11.5)	5 (1 to 14)	—	0 (−1.0 to 1.0)
Noninvasive	47 (30 to 63)	49 (28 to 62)	—	−1.0 (−7.0 to 5.0)
Time until full enteral feeding	10 (9 to 14)	12 (10 to 19)	—	−2.0 (−3.0 to −1.0)

* All listed outcomes were measured before discharge home unless otherwise specified. NA denotes not applicable.
† This confidence interval is two-sided. The 95% confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.
‡ This analysis was not prespecified in the trial protocol.
§ This analysis includes survivors at the time of assessment, which consisted of 115 patients in the expectant-management group and 111 in the early-ibuprofen group with available data.
¶ The values in this category are Hodges–Lehmann estimates.

data showing associations between ibuprofen use and the development of bronchopulmonary dysplasia[24,25] and is supported by in vitro and in vivo studies suggesting that angiogenesis may be inhibited by ibuprofen.[26,27] A recent prospective study showed decreased vascular growth factors in preterm infants with PDA after exposure to ibuprofen.[28] Of note, previous randomized trials have not shown an increase in the risk of bronchopulmonary dysplasia with ibuprofen treatment. It is possible that this discrepancy can be explained by the high percentage of in-

fants who received open-label treatment in the expectant-management group in these trials.[9,13]

Our exploratory analyses raise the possibility of a sex-related difference in the effects of the intervention on the primary outcome, which suggests a benefit specifically for male infants who received expectant management. However, this analysis was one of several secondary and subgroup analyses that were performed without adjustment for multiplicity, so the results may be explained by chance. Effect modification according to sex has not been reported in other trials, and further study is needed to confirm this finding.

Our trial focused on the short-term effects of PDA management in the neonatal period and cannot inform management beyond this period, including whether neonatal follow-up should include routine echocardiographic screening for potentially prolonged exposure to transductal left-to-right shunting. Although spontaneous closure of untreated PDA before discharge occurs in up to 85% of patients,[29] in a cohort of patients who had been discharged home with a PDA, 8.4% underwent assisted PDA closure at a median postnatal age of 349 days.[30]

Our trial has several limitations. The main limitation is that even though the investigators recruited infants at 17 centers for almost 4 years, enrollment was stopped after only 48% of the planned sample size had undergone randomization. However, we found that expectant management was noninferior to early ibuprofen, and indeed outcomes appeared to be worse in the ibuprofen group. The PDA diameter, which was used as an inclusion criterion, is an imperfect indicator of hemodynamically significant PDA,[31] even though it is the most commonly used measure to guide management.[11] Our trial was unblinded because it was designed to compare the two most commonly used strategies for PDA management. However, we consider bias to be unlikely in the assessment of the components of the composite primary outcome; in the six cases in which the classification of the severity of bronchopulmonary dysplasia involved clinician judgment because the indicated oxygen reduction test had not been performed, assessment was made by experts who were unaware of treatment assignments. In addition, the majority of enrolled infants were White and had a gestational age of more than 24 weeks at randomization. Because infants were recruited soon after birth, they did not have prolonged exposure to a moderate-to-large shunt, to invasive ventilation,

Table 4. Adverse Events.*

Event	Expectant Management (N=136)	Early Ibuprofen (N=137)
Adverse event		
Patients with at least one adverse event — no. (%)	7 (5.1)	8 (5.8)
Medical specialty — no. of events		
Cardiology		
Pulmonary stenosis	1	1
Ductus arteriosus reopening	0	1
Respiratory or ear, nose, and throat		
Glottic edema	1	0
Stridor	0	1
Vocal cord paralysis	0	1
Dermatology		
Wrist abscess	1	1
Cellulitis	1	0
Necrosis caused by extravasation	1	0
Surgical complication: wound dehiscence	0	2
Pharmacology: caffeine toxicity	1	0
Neurology: West syndrome†	0	1
Nephrology: severe dehydration from tubulopathy	1	0
Hematology: thrombus vena cava inferior	2	0
Serious adverse event		
Patients with at least one serious adverse event — no. (%)	3 (2.2)	4 (2.9)
Medical specialty — no. of events		
Respiratory: subglottic stenosis	0	1
Circulatory		
Pulmonary-vein stenosis	0	1
Aortic coarctation	1	0
Gastrointestinal		
Volvulus	1	0
Meconium ileus	0	2
Hematology: renal-vein thrombosis	0	1
Surgical: liver hemorrhage during laparotomy	1	0

* Patients could have more than one adverse event or serious adverse event.
† West syndrome is frequently associated with infantile spasms, hypsarrhythmia, and intellectual disability.

or both, so the results may not be generalizable to infants of different races or gestational ages or to those receiving prolonged invasive ventilation. In the intervention group, ibuprofen was administered according to local protocols. Although most centers used an initial intravenous ibuprofen dose of 10 mg per kilogram, followed by 5 mg per kilogram at 24 and at 48 hours after the first dose, higher-dose ibuprofen (15/7.5/7.5 to 20/10/10 mg per kilogram) may be more effective in inducing PDA closure.[10,32] However, the closure rate in our trial after a first course was similar to that in earlier randomized, controlled trials of ibuprofen treatment.[19,32,33]

The results of this trial should not be interpreted to suggest that there is no causal relationship between PDA and neonatal morbidity in extremely preterm infants. Pathophysiologically, a high transductal left-to-right shunt volume with subsequent pulmonary hyperperfusion and systemic hypoperfusion may indeed have adverse consequences; evidence suggests that prolonged shunt exposure is associated with development of bronchopulmonary dysplasia.[34,35] Rather, it is plausible that an attempt to close the PDA with ibuprofen may be more harmful than the condition itself. Safer and more effective treatments for a PDA with a high left-to-right shunt volume warrant study.

In this international multicenter trial involving extremely preterm infants with a gestational age below 28 weeks, expectant management for a PDA measuring more than 1.5 mm in diameter was noninferior to early ibuprofen treatment with regard to necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death, and results suggested a lower risk of this outcome in the expectant-management group.

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APPENDIX

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