1 Original Article

² Trial of Selective Early Treatment of Patent ³ Ductus Arteriosus with Ibuprofen

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26 Abstract

Background 27

The cyclooxygenase inhibitor ibuprofen may be used to treat patent ductus 28

arteriosus (PDA) in preterm infants. Whether selective early treatment of large 29

PDAs with ibuprofen would improve short-term outcomes is not known. 30

31 Methods

32 We conducted a multicenter, randomized, double-blind, placebo-controlled trial

- evaluating early treatment (\leq 72 hours after birth) with ibuprofen for a large PDA 33
- (diameter of \geq 1.5 mm with pulsatile flow) in extremely preterm infants (born 34

between 23 weeks 0 days' and 28 weeks 6 days' gestation). The primary outcome 35

was a composite of death or moderate or severe bronchopulmonary dysplasia 36

evaluated at 36 weeks of postmenstrual age. 37

38 Results

A total of 326 infants were assigned to receive ibuprofen and 327 to receive 39

- placebo; 324 and 322, respectively, had data available for outcome analyses. A 40
- primary-outcome event occurred in 220 of 318 infants (69.2%) in the ibuprofen 41
- 42 group and 202 of 318 infants (63.5%) in the placebo group (adjusted risk ratio,
- 43 1.09; 95% confidence interval [CI], 0.98 to 1.20; P=0.10). A total of 44 of 323
- infants (13.6%) in the ibuprofen group and 33 of 321 infants (10.3%) in the 44
- 45 placebo group died (adjusted risk ratio, 1.32; 95% CI, 0.92 to 1.90). Among the

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1 infants who survived to 36 weeks of postmenstrual age, moderate or severe

2 bronchopulmonary dysplasia occurred in 176 of 274 (64.2%) in the ibuprofen

3 group and 169 of 285 (59.3%) in the placebo group (adjusted risk ratio, 1.09;

4 95% CI, 0.96 to 1.23). Two serious adverse events occurred that were possibly

5 related to ibuprofen.

6 Conclusions

7 The risk of death or moderate or severe bronchopulmonary dysplasia at 36 weeks

8 of postmenstrual age was not significantly lower among infants who received

9 early treatment with ibuprofen than among those who received placebo. (Funded

10 by the National Institute for Health Research Health Technology Assessment

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Over the past two decades, survival among extremely preterm infants has 12 increased alongside modest reductions in neonatal morbidity, although the 13 incidence of bronchopulmonary dysplasia has increased.¹ In this gestation 14 group, a large (\geq 1.5 mm in diameter) patent ductus arteriosus (PDA) that 15 is present beyond 3 days of age is associated with higher mortality and 16 morbidity and a higher risk of bronchopulmonary dysplasia than have been 17 reported among infants without a PDA.² The incidence of PDA is inversely 18 proportional to gestational age at birth: more than 40% of infants born at 19 less than 28 weeks' gestation have persistent PDA by 4 months of age.^{3,4} The 20 risk of bronchopulmonary dysplasia or death in extremely preterm infants also 21 increases with the persistence of PDA beyond 1 to 2 weeks of age.⁵ 22 Various treatment strategies have been investigated for the management of 23 PDA.⁶ Prophylaxis with indomethacin or ibuprofen in the first 12 to 24 hours of 24 life has been reported to reduce the risk of severe intraventricular hemorrhage 25

26 and pulmonary hemorrhage but has not been found to increase survival without

²⁷ neurosensory impairment at 18 months.⁷ However, if a prophylactic approach

28 is used, many infants will receive treatment unnecessarily, since PDAs can

29 close spontaneously.8 Data on the treatment of infants with a symptomatic PDA

³⁰ are limited, and reports of improvements in clinical outcomes are lacking.⁹

31 Consequently, the number of extremely preterm infants with a PDA who are

32 treated pharmacologically has decreased.¹⁰

With the use of bedside functional echocardiography,¹¹ infants can now 33 be screened to identify large PDAs with unrestricted flow that are unlikely to 34 close spontaneously. Selective early targeted treatment of patients with these 35 PDAs may make it possible to avoid unnecessary treatment of all patients with 36 PDAs.¹² Parenteral indomethacin and ibuprofen have been used for early targeted 37 treatment of PDA, with no evidence of a difference in their efficacy,¹³ although 38 the side-effect profile of ibuprofen has been reported to be superior.⁶ 39 We hypothesized that among patients with a PDA of 1.5 mm or larger 40 in diameter with unrestricted flow identified with the use of bedside 41 echocardiography, early selective treatment (\leq 72 hours after birth) with 42

1 ibuprofen would reduce mortality and improve short-term outcomes such as

2 bronchopulmonary dysplasia to a greater extent than placebo.

3 Methods

4 Trial Design

5 We conducted a multicenter, double-blind, randomized, placebo-controlled trial

6 in 32 neonatal intensive care units in the United Kingdom in accordance with

 $^{7}\,$ a published protocol (available with the full text of this article at NEJM.org). $^{14}\,$

8 The main trial was preceded by an internal pilot phase to assess the suitability

9 of trial procedures and recruitment. The clinicians, the infants' families,

10 and the persons who assessed outcomes were unaware of the randomization

11 assignments.¹⁴ The trial was coordinated by the National Perinatal Epidemiology

12 Unit (NPEU) Clinical Trials Unit at the University of Oxford, United Kingdom

13 (which was responsible for the conduct of the trial), and was overseen by the

14 trial steering committee, acting on the recommendations of an independent

15 data and safety monitoring committee. Additional details are provided in the

16 Supplementary Appendix, available at NEJM.org.

17 Patients

18 After written informed consent was obtained from the parents, infants born

19 between 23 weeks 0 days' and 28 weeks 6 days' gestation who were less than

20 72 hours old, were confirmed by echocardiography to have a large PDA, and

21 for whom there were no associated clinical concerns for acute pulmonary

22 hypertension were considered to be eligible for participation. A large PDA

²³ was defined as a PDA with a diameter of at least 1.5 mm and unrestricted

24 transductal pulsatile (left-to-right shunting) flow. A full list of the inclusion and

25 exclusion criteria is provided in Table S1 in the Supplementary Appendix.

26 Randomization

27 Dynamic randomization was performed with a secure Web-based system that

28 was created and hosted by the NPEU Clinical Trials Unit with 24/7 telephone

29 backup, ensuring concealment of the group assignments. The randomization

30 program used a probabilistic minimization algorithm and assigned patients

31 in a 1:1 ratio to one of the two groups to ensure balance with respect to the

32 size of the PDA, gestational age at birth, age, sex, trial site, whether the infant

33 was from a multiple birth, mode of respiratory support, and whether inotropes

34 were received. Infants in multiple births underwent randomization individually.

³⁵ Participants were enrolled by the delegated clinician at the trial site.¹⁴

36 Intervention and Trial Procedures

37 The trial intervention was ibuprofen sodium, and the matched placebo was a

38 clear sterile solution of 0.9% sodium chloride. Each carton containing ibuprofen

³⁹ or placebo was labeled with a unique code in compliance with the guidance

40 provided in annex 13 of the European Commission guidelines for Good

41 Manufacturing Practice. Ibuprofen was administered parenterally as a loading

1 dose of 10 mg per kilogram of body weight, followed by two doses of 5 mg per

2 kilogram at least 24 hours apart. Placebo was administered as an equal volume

3 of 0.9% sodium chloride (Table S2). Only one course of ibuprofen or placebo

4 was given. Prespecified criteria for open-label medical or surgical treatment after

5 enrollment are shown in Table S3.

6 Transthoracic echocardiography was performed to assess eligibility within 72

7 hours after birth and at 3 weeks (18 to 24 days) of age to assess the patency of

8 the PDA while minimizing open-label treatment. For quality control, a sample

9 of echocardiograms from 65 infants was reviewed independently by a pediatric

10 echocardiographer who was unaware of the treatment assignments.

11 Outcomes

12 The primary outcome was a composite of death or moderate or severe

13 bronchopulmonary dysplasia assessed at 36 weeks of postmenstrual age¹⁵ (Tables

14 S4 and S5). A physiological challenge of supplemental oxygen reduction was

15 used to test for oxygen need at 36 weeks of postmenstrual age¹⁶ to differentiate

16 mild from moderate bronchopulmonary dysplasia (Fig. S1). Secondary short-

17 term outcomes up to the time of discharge included individual components

18 of the primary outcome, the severity of bronchopulmonary dysplasia, severe

19 intraventricular hemorrhage, cystic periventricular leukomalacia, retinopathy of

20 prematurity requiring treatment, clinically significant pulmonary hemorrhage,

21 acute pulmonary hypertension, definitive necrotizing enterocolitis, closed or

22 clinically nonsignificant PDA less than 1.5 mm in diameter with restricted

23 flow at 3 weeks age, open-label treatment of a PDA causing symptoms, weight

24 gain, and discharge home while receiving supplemental oxygen (Table S5).¹⁴

25 Other secondary short-term outcomes are listed in the Supplementary Appendix

²⁶ and in the statistical analysis plan (available with the protocol).¹⁷ All outcome

27 data were recorded routinely, including demographic data and complications

28 of prematurity; these data were obtained from clinical notes or trial-related29 assessments (Table S6).

{q1}A list of foreseeable serious adverse events that are common in this
patient population was prespecified (see section 9.1.4 in the protocol);

32 unforeseeable serious adverse events were defined as those that were not

33 included on this list. A serious adverse reaction was defined as a serious adverse

34 event that was considered to have been caused by the administration of the trial

- 35 agent; if such an event was not consistent with the safety profile of the trial
- ³⁶ agent, it was classed as a suspected unexpected serious adverse reaction.¹⁴

37 Statistical Analysis

38 The incidence of the primary outcome was predicted to be 60% in the placebo

³⁹ group (see Supplementary Methods). A sample of 730 infants was calculated

40 to be required in order to detect a clinically important absolute risk reduction

41 of 12 percentage points (i.e., an incidence of 60% in the placebo group and an

42 incidence of 48% in the ibuprofen group) with 90% power and a type I error of

43 5% under the assumption that 1% of infants would be lost to follow-up.¹⁴

Analyses were performed according to the intention-to-treat principle, with 1 infants excluded from the analysis only if their data were missing. Missing data 2 were not imputed. Analyses were adjusted for minimization factors, such as the 3 size of the PDA at randomization, gestational age at birth, age at randomization, 4 sex, whether the infant was from a multiple birth, mode of respiratory support 5 at randomization, whether inotropes were received at the time of randomization, 6 and trial site, as well as for the correlation between siblings from multiple 7 8 births, when technically possible (Table S7). Center was treated as a random effect in the models, and all other factors were treated as fixed effects. Binary 9 outcomes were analyzed by means of mixed-effects Poisson regression with a 10 robust variance estimator; risk ratios and 95% confidence intervals are reported. 11 The assumptions used in the models were assessed and found to be valid (Fig. 12 S2). Continuous outcomes were analyzed with the use of linear regression 13 models; mean differences and 95% confidence intervals (after checking model 14 assumptions) are reported. Because of the large number of short-term outcomes, 15 statistical inference was restricted to a prespecified short list (Table S5). No 16 formal method to adjust for multiplicity was used; the widths of the confidence 17 intervals have not been adjusted for multiplicity, and inferences drawn may not 18 be reproducible and should not be used to infer definitive treatment effects for 19 secondary outcomes. Full details of the statistical analysis are provided in the 20 statistical analysis plan.¹⁷ Additional details are provided in the Supplementary 21 Appendix. Stata/SE, version 15 (StataCorp), was used for all analyses. 22

2 Appendix. Stata/SE, version 15 (stataCorp), was used for an a

23 **Results**

24 Patients

From July 2015 through December 2020, a total of 653 infants underwent 25 randomization: 326 were assigned to receive ibuprofen and 327 to receive 26 placebo. A total of 22 infants underwent randomization during the internal 27 pilot phase and 631 during the main recruitment phase (Fig. 1). Maternal and 28 infant baseline characteristics appeared to be well balanced between the groups 29 (Table 1 and Table S8). The median PDA diameter was 2.2 mm (interquartile 30 range, 1.9 to 2.6). An independent audit of the echocardiograms indicated that 31 93.8% of infants who underwent randomization in the trial met the prespecified 32 echocardiographic eligibility criteria. The remainder of the echocardiographic 33 images could not be assessed accurately to confirm the eligibility criteria. 34 A total 318 of 326 infants (97.5%) in the ibuprofen group and 315 of 327 35 (96.3%) in the placebo group received their assigned intervention (Fig. 1). 36 Parental consent to use the data from 7 infants was withdrawn, which left data 37 from 324 infants in the ibuprofen group and 322 in the placebo group available 38 for outcome analyses. Data that were required to assess the primary outcome 39 were missing for an additional 10 infants, and therefore assessment of the 40 primary outcome was possible for 318 infants (97.5%) in the ibuprofen group 41 and 318 (97.2%) in the placebo group (Fig. 1). 42

1 Outcomes

2 A primary-outcome event (death or moderate or severe bronchopulmonary

- 3 dysplasia assessed at 36 weeks of postmenstrual age) occurred in 220 of 318
- infants (69.2%) assigned to ibuprofen and 202 of 318 infants (63.5%) assigned to 4
- placebo (adjusted risk ratio, 1.09; 95% CI, 0.98 to 1.20; P=0.10) (Table 2). A total 5
- of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 (10.3%) in 6
- the placebo group died (adjusted risk ratio, 1.32; 95% CI, 0.92 to 1.90). Among 7
- 8 the infants who survived to 36 weeks of postmenstrual age, moderate or severe
- bronchopulmonary dysplasia was present in 176 of 274 (64.2%) in the ibuprofen 9
- group and 169 of 285 (59.3%) in the placebo group (adjusted risk ratio, 1.09; 10
- 95% CI, 0.96 to 1.23) (Table 2). Results for the primary outcome excluding 11

12 infants who received open-label medical treatment without meeting the specified criteria are shown in Tables S9 and S10. 13

A closed or small PDA (<1.5 mm in diameter) at 3 weeks (18 to 24 days) of 14 age was present in 176 of 317 infants (55.5%) in the ibuprofen group and 117 15 of 316 (37.0%) in the placebo group (adjusted risk ratio, 1.50; 95% CI, 1.30 to 16 1.74) (Table 2 and Table S11). After randomization, 571 of 646 infants (88.4%) 17 received all three doses of ibuprofen or placebo (Table 3). 18

Additional secondary outcomes are shown in Table 2 and Table S13. A total 19

- of 43 infants (13.3%) in the ibuprofen group and 82 (25.5%) in the placebo 20
- group received open-label medical treatment for symptoms attributable to a PDA; 21
- 9 (2.8%) and 31 (9.6%), respectively, received surgical treatment (Table 2). The 22
- percentage of infants who received any open-label treatment (for any indication), 23
- including surgical ligation, was 14.2% in the ibuprofen group and 29.8% in the 24
- placebo group; the median interval from randomization to open-label treatment 25
- was 11 days (interquartile range, 8 to 17) and 12 days (interquartile range, 7 to 26
- 21), respectively (Table S12 and Fig. S5). Prespecified subgroup analyses of the 27
- composite primary outcome and its components are shown in Figure 2A and 28 Figures S3 and S4. An additional prespecified subgroup analysis of the risk of
- 29 severe necrotizing enterocolitis (Bell's stage \geq II) according to the diameter of the
- 30
- PDA at randomization is shown in Figure 2B. 31

Safety 32

[q2]Two serious adverse events occurred that were assessed as possibly related to 33 ibuprofen; one of these events was classified as a suspected unexpected serious 34 adverse reaction (Table S15). An additional four unforeseeable serious adverse 35 events that were assessed as not related to ibuprofen occurred in the ibuprofen 36 group. Two unforeseeable serious adverse events occurred in the placebo group, 37 both of which were assessed as not related to placebo. Foreseeable serious 38 adverse events were reportable during the period between the first dose of 39 ibuprofen or placebo and 7 days after the last dose (Table S14). 40

1 Discussion

2 In this double-blind, randomized, placebo-controlled trial involving extremely preterm infants with a large PDA, we found no evidence that early treatment 3 with ibuprofen was associated with a lower incidence of death or moderate 4 or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age than 5 placebo. There was no significant between-group difference in either the risk of 6 death or the risk of moderate or severe bronchopulmonary dysplasia. 7 Our results are broadly consistent with those of other studies of early targeted 8 treatment of PDA with ibuprofen that have not shown a convincing benefit with 9 respect to clinical outcomes.^{12,18-21} Although these studies have shown a reduced 10 risk of pulmonary hemorrhage and patient symptoms attributable to the PDA, 11 intervention with ibuprofen was not shown to be associated with a reduction in 12 the incidence of bronchopulmonary dysplasia, death, or neurodisability.^{18,19} 13 Approximately half the infants we enrolled were born at less than 26 weeks' 14 gestation, the cohort at greatest risk for a hemodynamically significant PDA. 15 We enrolled infants who had a large PDA as determined on the basis of a 16 combination of echocardiographic measures, including the diameter of the PDA 17 and ductal flow characteristics.^{22,23} The incidence of death or moderate or severe 18 bronchopulmonary dysplasia in our trial was high but was similar to that in 19 other randomized trials of early pharmacologic treatment of PDA.^{18,19,21} 20 A single early course of ibuprofen resulted in a closed or small PDA 21 (confirmed by echocardiography at 3 weeks of age) in only 55.5% of infants who 22 were assigned to receive ibuprofen. Although previous studies have reported 23 variable closure rates with early intravenous ibuprofen therapy,²⁴ our findings are 24 consistent with recent trials involving similar patient populations.^{18,21,25} Variation 25 in the rate of PDA closure among studies is likely to be caused by differences 26 in the timing of the intervention, an open-label study design, the route of 27 administration of the ibuprofen, and the dosing regimen used.^{6,26} Intravenous 28 ibuprofen administered within a standard dosing regimen was chosen as the 29 intervention in our trial because higher doses are usually used only when 30 an infant is 7 days of age or older, and it was the most common treatment 31 schedule for infants with a PDA in the United Kingdom at the time the trial 32 was designed.²⁷ Similarly, most units did not routinely repeat echocardiographic 33 assessment after ibuprofen therapy with the intention of offering a second 34 course if the PDA remained patent. 35 Open-label medical therapy for a symptomatic PDA appeared to be less 36

common in this trial than in other, similar trials²⁸ and occurred almost twice as frequently in the placebo group as in the ibuprofen group. Although a recent noninferiority trial of early ibuprofen treatment in the management of PDA showed a very low percentage of patients (0.7%) receiving open-label medical therapy in the expectant management group,¹⁹ there was frequent use of acetaminophen as an analgesic after randomization in both groups. Accordingly, exposure to any pharmacologic agent with the potential for ductal closure 1 was approximately 25% among infants who received expectant management, a

2 percentage similar to that in our trial.

The median time from randomization to open-label medical therapy in our 3 trial was 11 to 12 days, well beyond the time when the infant had received 4 5 the trial intervention (up to 7 days). This was much later than the timing of rescue treatment in a French trial¹⁸ (median of 4 days) that overlapped with the 6 trial intervention. The low percentage of infants with effective closure in the 7 8 ibuprofen group in our trial combined with the relatively late timing of openlabel medical therapy suggests that a large percentage of treated infants may 9 have been exposed to the potentially damaging effects of the ductal shunt for 10 prolonged period. Combined with the relatively high percentage of patients а 11 in the placebo group who received open-label medical therapy (30%), this 12 resulted in poor discrimination between the two groups with respect to ductal 13 patency (55.5% vs. 37.0%) and probably also in prolonged exposure to a ductal 14 shunt. The absence of data from serial echocardiograms precludes detailed 15 analysis and limits interpretation of the effect of shunt duration on outcomes 16 in the two groups. Nevertheless, one might reasonably conclude that the early, 17 echocardiography-targeted course of ibuprofen used in our trial resulted in a 18 percentage of infants with PDA closure or constriction that was 18 percentage 19 points higher than that obtained with placebo, without affecting clinical 20 outcomes. 21

We found no evidence that ibuprofen resulted in excess serious complications. 22 Unlike Hundscheid et al. in the BeNeDuctus trial,¹⁹ we did not identify an 23 association between ibuprofen therapy and bronchopulmonary dysplasia, a 24 finding that might be explained by differences in the trial populations or drug 25 exposure. Whereas most of the infants enrolled in our trial were receiving 26 invasive ventilation, the BeNeDuctus trial mostly enrolled infants who were 27 receiving noninvasive respiratory support. Another important difference was the 28 use of repeated courses (often with high doses) of ibuprofen in the BeNeDuctus 29 trial. Early exposure to high cumulative doses of ibuprofen in infants with a 30 relatively low baseline risk of bronchopulmonary dysplasia, as in that trial, may 31 be detrimental. 32

Our trial has limitations. In spite of strict criteria to restrict its use, open-33 34 label medical therapy was received by 29.8% of the infants in the placebo group, the likely effect of which would have been to increase the percentage of infants 35 with PDA closure in this group and make it more difficult to identify between-36 group differences in clinical outcomes. We did not meet our enrollment goal of 37 730 patients, in part because of drug nonavailability, changes in clinical practice, 38 competing trials, and the effect of the coronavirus disease 2019 pandemic. 39 Although early assessment and randomization were encouraged, the median age 40 41 at which the first dose of ibuprofen or placebo was administered was 61 hours, which was later than in other, similar trials.^{18,20} Trial entry was permitted up to 42

43 72 hours after birth to allow a pragmatic approach to enrollment and to ensure

- 1 the availability of an echocardiographic assessment. However, it is possible that
- 2 earlier intervention would have achieved more effective ductal closure.^{24,29}
- 3 Among extremely preterm infants with a large PDA, we found no evidence
- 4 that early treatment with ibuprofen was associated with a lower risk of death
- 5 or moderate or severe bronchopulmonary dysplasia than placebo at 36 weeks of
- 6 postmenstrual age.

Disclaimer

- 7 The views expressed are those of the authors and not necessarily those of the National Institute for
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Data sharing

- 9 A data sharing statement provided by the authors is available with the full text of this article at
- 10 NEJM.org.

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12 Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Quick Take Video

General comments on video or navigation (use sticky notes and include timecode):

Early Treatment of Patent Ductus Arteriosus with Ibuprofen

DOI: NEJMdo007368

View video and metadata on JW Player (https://content.jwplatform.com/previews/)

Multimedia Blurb

1 Early Treatment of Patent Ductus Arteriosus with Ibuprofen

- 2 For extremely preterm infants who have a large patent ductus arteriosus, early treatment with
- 3 ibuprofen may reduce the risk of death and improve short-term outcomes. New research findings
- 4 are summarized in a short video.

Marginal note for print A Quick Take is available at NEJM.org



Figure 1. Screening, Randomization, and Inclusion in the Analyses.



Figure 2. Subgroup Analyses of the Primary Outcome and Severe Necrotizing Enterocolitis.

Panel A shows the subgroup analysis of the primary outcome, a composite of death or moderate or severe bronchopulmonary dysplasia assessed at 36 weeks of postmenstrual age. Panel B shows the subgroup analysis of severe necrotizing enterocolitis, defined as necrotizing enterocolitis of Bell's stage II or higher, as confirmed by radiography, histopathological analysis, or both. Stages in the Bell classification system for necrotizing enterocolitis range from I to III, with higher stages indicating more severe illness. In {q3}each panel, the diamond and dashed line indicate the overall measure of effect, and the width of the diamond indicates the 95% confidence interval of the overall effect. Risk ratios and 95% confidence intervals were obtained from an interaction term between treatment assignment and subgroup characteristic of interest in a log binomial model adjusted for the size of the patent ductus arteriosis (PDA) at randomization, gestational age at birth, age at randomization, sex, whether the infant was from a multiple birth, mode of respiratory support at randomization, whether inotropes were received at randomization, and trial site as a random effect; data from siblings were clustered to account for correlation between infants in multiple births. Some of the patient subgroups have been collapsed into fewer subgroups than prespecified because of the small number of patients in each category. No adjustments were made for multiplicity of testing, and therefore interpretation of the confidence intervals should not be used to assess treatment effect.

Table 1. Baseline Characteristics of the Infants and Their Mothers,*			
Characteristic	Ibuprofen (N=324)	Placebo (N = 322)	
Maternal characteristics			
Race_ — no./total no. (%)†			
White	223/299 (74.6)	223/303 (73.6)	
Asian	39/299 (13.0)	45/303 (14.9)	
Black	25/299 (8.4)	25/303 (8.3)	
Other	12/299 (4.0)	10/303 (3.3)	
Age — yr	30.1±6.5	30.2±6.2	
Infant characteristics at randomization			
Median postnatal age (IQR) — hr ‡	57.5 (43.1–65.6)	56.8 (43.9–66.7)	
Postnatal age distribution — no. (%)			
<12 hr	2 (0.6)	2 (0.6)	
12 to <24 hr	15 (4.6)	14 (4.3)	
24 to <48 hr	90 (27.8)	89 (27.6)	
48 to <72 hr	217 (67.0)	217 (67.4)	
Gestational age — wk‡	26.1±1.5	26.1±1.6	
Mode of birth — no. (%)			
Vaginal birth, cephalic	141 (43.5)	138 (42.9)	
Vaginal birth, breech	50 (15.4)	46 (14.3)	
Cesarean section before onset of labor	83 (25.6)	80 (24.8)	
Cesarean section after onset of labor	50 (15.4)	58 (18.0)	
Birth weight — g	839.9±204.8	852.9±211.3	
Male sex — no. (%)‡	180 (55.6)	175 (54.3)	
Apgar score 5 min after birth			
Median score (IQR)	8.0 (6.0–9.0)	7.0 (6.0–9.0)	
No. of patients with data	278	288	
Median diameter of PDA (IQR) — mm‡	2.2 (1.9–2.5)	2.2 (1.9–2.6)	
Distribution of PDA diameters — no. (%),			
≥1.5 mm and <2.0 mm	84 (25.9)	82 (25.5)	
≥2.0 mm and <3.0 mm	201 (62.0)	201 (62.4)	
≥3.0 mm	39 (12.0)	39 (12.1)	
Mode of respiratory support — no. (%)‡			
Invasive ventilation with endotracheal tube	206 (63.6)	204 (63.4)	
Noninvasive respiratory support only∬	116 (35.8)	115 (35.7)	
No mechanical ventilation or pressure support¶	2 (0.6)	3 (0.9)	
Receipt of inotropes — no. (%)‡	44 (13.6)	37 (11.5)	

* Plus-minus data are means ±SD. IQR denotes interquartile range, and PDA patent ductus arteriosus.

 \dagger Race was reported by the mothers,

the characteristic was a factor used in the randomization minimization algorithm.

🖇 This category included nasal continuous positive airway pressure, nasal ventilation, humidified high-flow nasal cannula therapy, or low-flow oxygen (≥1.1 liters per minute). ¶This category included low-flow oxygen (<1.1 liters per minute) and ambient oxygen.

Table 2. Primary and Secondary Outcomes.					
Outcome	lbuprofen (N=324)	Placebo (N = 322)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*	
Primary outcome: death or moderate or severe bronchopulmonary dysplasia assessed at 36 wk of postmenstrual age — no./total no. (%)†	220/318 (69.2)	202/318 (63.5)	1.09 (0.97–1.22)	1.09 (0.98–1.20)‡	
Secondary outcomes					
Death by 36 wk of postmenstrual age — no./total no. (%)	44/323 (13.6)	33/321 (10.3)	1.33 (0.87–2.02)	1.32 (0.92–1.90)	
Survival to 36 wk of postmenstrual age — no. of infants	280	289			
Moderate or severe bronchopulmonary dysplasia at 36 wk of postmenstrual age — no./total no. (%)	176/274 (64.2)	169/285 (59.3)	1.08 (0.95–1.23)	1.09 (0.96–1.23)	
Any intraventricular hemorrhage — no. (%)	137 (42.3)	132 (41.0)			
Grade I or II without ventricular dilatation	92 (28.4)	98 (30.4)			
Grade III or IV with ventricular dilatation or intraparenchy- mal abnormality∬	45 (13.9)	34 (10.6)	1.32 (0.87–2.00)	1.30 (0.93–1.82)	
Cystic periventricular leukomalacia — no. (%)	15 (4.6)	9 (2.8)	1.66 (0.74–3.73)	1.62 (0.69-3.83)	
Treatment for retinopathy of prematurity in at least one eye — no. (%)	45 (13.9)	45 (14.0)	0.99 (0.68–1.46)	0.98 (0.68–1.42)	
Clinically significant pulmonary hemorrhage — no./total no. (%)¶	24/322 (7.5)	18/322 (5.6)	1.33 (0.74–2.41)	1.39 (0.70–2.77)	
Treatment for acute pulmonary hypertension with pulmonary vasodilator — no. (%)	17 (5.2)	16 (5.0)	1.05 (0.54–2.05)	1.04 (0.51–2.13)	
Severe necrotizing enterocolitis — no./total no. (%)	41/323 (12.7)	41/322 (12.7)	1.00 (0.67–1.49)	1.01 (0.67–1.51)	
PDA closed or <1.5 mm at 3 wk of age, confirmed by echocar- diography — no./total no. (%)**	176/317 (55.5)	117/316 (37.0)	1.50 (1.26–1.79)	1.50 (1.30–1.74)	
PDA ≥1.5 mm at 3 wk of age, not treated medically or by surgi- cal closure — no./total no. (%)**	74/321 (23.1)	109/317 (34.4)	0.67 (0.52–0.86)	0.67 (0.53–0.85)	
Open-label surgical treatment of a symptomatic PDA — no. (%)	9 (2.8)	31 (9.6)	0.29 (0.14–0.60)	0.29 (0.18–0.47)	
Discharged home with supplemental oxygen — no. (%)	130 (41.3)	123 (39.2)	1.05 (0.87–1.27)	1.06 (0.92–1.22)	
Weight gain					
No. of infants with data	257	265			
Mean change in z score between birth and discharge	$-1.0{\pm}1.0$	-1.1±1.0	0.1 (-0.1 to 0.2)††	0.1 (-0.1 to 0.2)††	

* Adjusted for minimization factors (size of the PDA, gestational age at birth, age at randomization, sex, trial site, whether the infant was from a multiple birth, mode of respiratory support at randomization, and whether inotropes were received at the time of randomization) and the correlation between siblings from multiple births, where technically possible. Trial site was treated as a random effect in the models, and all other factors as fixed effects.

† In the placebo group, 1 infant was withdrawn before 36 weeks and 3 did not have information on oxygen requirement available at 36 weeks. In the ibuprofen group, 1 infant was lost to follow-up before 36 weeks and 5 did not have information on oxygen requirement available at approximately 36 weeks.

‡ P=0.10.

Severe intraventricular hemorrhage was defined as grade III or IV.

¶ Fresh blood in endotracheal tube with increase in respiratory support.

Severe necrotizing enterocolitis was defined as Bell's stage II or higher as confirmed by radiography, histopathological analysis, or both. Stages in the Bell classification system for necrotizing enterocolitis range from I to III, with higher stages indicating more severe illness.

** Echocardiography was planned to be performed at 3 weeks (18 to 24 days) after birth to assess the patency of the PDA.

†† Value is the mean difference (95% confidence interval).

Table 3. Process Outcomes.		
Outcome	Ibuprofen (N=324)	Placebo (N = 322)
Did not receive assigned intervention — no. (%)	7 (2.2)	11 (3.4)
Did not receive all doses of ibuprofen or placebo — no. (%)	41 (12.7)	34 (10.6)
Doses received — no. (%)		
0	7 (2.2)	9 (2.8)
1	17 (5.2)	11 (3.4)
2	17 (5.2)	14 (4.3)
3	283 (87.3)	288 (89.4)
Reason for early discontinuation — no./total no. (%)*		
Clinical decision	38/41 (92.7)	26/34 (76.5)
Parental request	0	1/34 (2.9)
Infant death	2/41 (4.9)	2/34 (5.9)
Missed dose or doses in error	1/41 (2.4)	2/34 (5.9)
Intervention window outside of trial period	0	2/34 (5.9)
Transfer out of recruiting site	0	1/34 (2.9)
Median age at first dose (IQR) — hr†	61 (47-68)	61 (48–69)
Distribution of median age at first dose — no. (%)		
0 to <24 hr	14/316 (4.4)	14/313 (4.5)
24 to <48 hr	68/316 (21.5)	65/313 (20.8)
48 to <72 hr	220/316 (69.6)	225/313 (71.9)
≥72 hr	14/316 (4.4)	9/313 (2.9)
Received second or third dose outside of dosing window — no./total no. (%)	5/297 (1.7)	4/301 (1.3)
Echocardiography not performed at 3 wk of age — no./total no. (%)‡	65/291 (22.3)	60/301 (19.9)
Oxygen reduction test not performed when infant was eligible — no./total no. (%)§	13/86 (15.1)	13/94 (13.8)

* Early discontinuation was defined as discontinuation when fewer than three doses had been received.

 The median was assessed among infants who had received at least one dose.
 The chocardiography was planned to be performed at 3 weeks (18 to 24 days) after birth to assess the patency of the PDA; infants who died before the 3-week echocardiogram could be obtained were excluded (33 infants in the ibuprofen group) and 21 in the placebo group).

§ Denominators are the numbers of infants who were eligible for the test.

Queries

q1. AU: Added text here accurate?

q2. AU: Text in this subsection OK as revised?

q3. AU: Added sentence correct?

Running head

1 Early Treatment of Patent Ductus Arteriosus with Ibuprofen

TWeek blurb

2 Early Treatment of Patent Ductus Arteriosus with Ibuprofen

- 3 Early treatment with ibuprofen for a large PDA did not result in a lower risk of death or moderate
- 4 or severe bronchopulmonary dysplasia than placebo at 36 weeks of postmenstrual age.

Social media image

5 Table 2

NEJM Topics

- 6 Cardiology
- 7 Cardiology General

Data Sharing Statement

Gupta S, Subhedar NV, Bell JL, et al. Trial of Selective Early Treatment of Patent Ductus Arteriosus with Ibuprofen. N Engl J Med. DOI: 10.1056/NEJMoa2305582.

Question	Authors' Response
Will the data collected for your study	Yes
be made available to others?	
Would you like to offer context for	—
your decision?	
Which data?	Complete de-identified patient data set
Additional information about data	-
How or where can the data be	pollyanna.hardy@npeu.ox.ac.uk
obtained?	
When will data availability begin?	Beginning Date:With publication
When will data availability end?	End Date:5 years after completion of trial
Will any supporting documents be	-
available?	
Which supporting documents?	Informed Consent Form
Additional information about	-
supporting documents	
How or where can supporting	https://www.npeu.ox.ac.uk
documents be obtained?	
When will supporting documents	Beginning Date:Now
availability begin?	
When will supporting documents	End Date:5 years after completion of trial
availability end?	
To whom will data be available?	Researchers whose proposed use of the data has
	been approved
For what type of analysis or purpose?	Secondary analysis if data use is approved
By what mechanism?	After approval of proposal, or with a signed data
	access agreement investigator involvement will
	depend on the discussion and agreement that is
	reached for the use of the data.
Any other restrictions?	None
Additional information	No

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