Association Between Early Screening for Patent Ductus Arteriosus and In-Hospital Mortality Among Extremely Preterm Infants

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**IMPORTANCE** There is currently no consensus for the screening and treatment of patent ductus arteriosus (PDA) in extremely preterm infants. Less pharmacological closure and more supportive management have been observed without evidence to support these changes.

**OBJECTIVE** To evaluate the association between early screening echocardiography for PDA and in-hospital mortality.

**DESIGN, SETTING, AND PARTICIPANTS** Comparison of screened and not screened preterm infants enrolled in the EPIPAGE 2 national prospective population-based cohort study that included all preterm infants born at less than 29 weeks of gestation and hospitalized in 68 neonatal intensive care units in France from April through December 2011. Two main analyses were performed to adjust for potential selection bias, one using propensity score matching and one using neonatal unit preference for early screening echocardiography as an instrumental variable.

**EXPOSURES** Early screening echocardiography before day 3 of life.

**MAIN OUTCOMES AND MEASURES** The primary outcome was death between day 3 and discharge. The secondary outcomes were major neonatal morbidities (pulmonary hemorrhage, severe bronchopulmonary dysplasia, severe cerebral lesions, and necrotizing enterocolitis).

**RESULTS** Among the 1513 preterm infants with data available to determine exposure, 847 were screened for PDA and 666 were not; 605 infants from each group could be paired. Exposed infants were treated for PDA more frequently during their hospitalization than nonexposed infants (55.1% vs 43.1%; odds ratio [OR], 1.62 [95% CI, 1.31 to 2.00]; absolute risk reduction [ARR] in events per 100 infants, −12.0 [95% CI, −17.3 to −6.7]). Exposed infants had a lower hospital death rate (14.2% vs 18.5%; OR, 0.73 [95% CI, 0.54 to 0.98]; ARR, 3.3 [95% CI, 0.4 to 6.3]) and a lower rate of pulmonary hemorrhage (5.6% vs 8.9%; OR, 0.60 [95% CI, 0.38 to 0.95]; ARR, 3.3 [95% CI, 0.4 to 6.3]). No differences in rates of necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions were observed. In the overall cohort, instrumental variable analysis yielded an adjusted OR for in-hospital mortality of 0.62 [95% CI, 0.37 to 1.04].

**CONCLUSIONS AND RELEVANCE** In this national population-based cohort of extremely preterm infants, screening echocardiography before day 3 of life was associated with lower in-hospital mortality and likelihood of pulmonary hemorrhage but not with differences in necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions. However, results of the instrumental variable analysis leave some ambiguity in the interpretation, and longer-term evaluation is needed to provide clarity.


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Closure of the ductus arteriosus is completed in most normal-term infants within 72 hours of birth. However, failure to close is common in extremely premature infants, resulting in a condition called patent ductus arteriosus (PDA). The hemodynamic consequences of PDA are a left-to-right shunt, resulting in high pulmonary blood flow and low systemic output. Clinical problems associated with this shunt are pulmonary hemorrage, hypotension, intraventricular hemorrhage, necrotizing enterocolitis, and mortality.\(^1\)\(^2\)

Ductal constriction can be induced in preterm infants through medical intervention with cyclooxygenase inhibitors. However, the optimal management of PDA continues to be debated because numerous randomized clinical trials have failed to demonstrate any benefit of treatment on survival and long-term outcome.\(^2\)\(^3\) However open-label rescue treatments were authorized in all these trials, hindering any conclusions about the effects of untreated PDA, even if spontaneous closure occurred in some extremely preterm infants.\(^4\) With a lack of consensus\(^5\) reflecting a low level of proof, the management of PDA is highly variable among neonatal intensive care units (NICUs). Some neonatologists have been opting for conservative treatment of PDA, although there is no evidence to support this approach.\(^6\) Others perform early screening echocardiography for PDA, which allows the diagnosis and treatment of PDA at a preclinical stage. A recent randomized clinical trial\(^6\) based on this strategy showed that early targeted indomethacin treatment reduced the rate of pulmonary hemorrage.

Observational studies are another way to evaluate a complex strategy.\(^7\) EPIPAGE 2 (Etude Épidémiologique sur les Petits Ages Gestationnels 2),\(^8\) a national population-based prospective cohort study, provided a unique opportunity to evaluate the association between early screening echocardiography for PDA and in-hospital morbidity and mortality in unselected preterm infants born before 29 weeks of gestational age and hospitalized in unselected NICUs. We hypothesized that early screening echocardiography for PDA would be associated with more frequent PDA treatment and better outcome.

### Methods

#### Study Cohort

The EPIPAGE 2 study is a national, prospective, population-based cohort study conducted in France in 2011. Recruitment took place at birth in all maternity units in France from April 2011 through December 2011, during an 8-month period for births occurring at 24 to 26 weeks and a 6-month period for births occurring at 27 to 28 weeks. The follow-up of participants is planned up to 2023. For this study, eligible children were those born at 24 to 28 weeks of gestation, admitted to the NICUs, alive at day 3, and with available information regarding whether an echocardiogram was performed, and if so, the timing and indication of the first echocardiographic assessment (screening or because of clinical signs).

### Ethics

Recruitment and data collection occurred only after families had received information and agreed to participate in this cohort by oral informed consent. The study was approved by the National Data Protection Authority, by the consultative committee on the treatment of information on personal health data for research purposes and the committee for the protection of people participating in biomedical research.

### Ductus Arteriosus Screening

Preterm infants were placed into 2 groups based on whether they had undergone early (before day 3) screening (not because of PDA-related clinical signs) echocardiography. Those who had undergone this procedure were classified as exposed to early PDA screening echocardiography. The optimal timing for screening echocardiography is unknown; 3 days was chosen based on a prior trial of PDA treatment and clinical feasibility.\(^9\) Infants who had not undergone early screening were classified as nonexposed. All data were prospectively collected during NICU hospitalization. Information was collected about ductus arteriosus diagnosis, including PDA markers from the echocardiography (ductus arteriosus diameter >1.5 mm),\(^10\) high-velocity flow in the left pulmonary artery (mean velocity >0.4 m/s or end-diastolic velocity >0.2 m/s),\(^11\) diastolic aortic flow reversal\(^12\) or low superior vena cava flow (<40 mL/kg/min),\(^13\) pulsatile ductus shunt flow pattern,\(^14\) date of treatment with ibuprofen or surgical ligation, and indication for treatment.

### Outcomes

The primary outcome was death between day 3 and discharge. The secondary outcomes were major neonatal morbidities: pulmonary hemorrhage; severe bronchopulmonary dysplasia, defined as a need for oxygen for at least 28 days plus a need for oxygen concentration 30% or greater, mechanical ventilator support, or continuous positive airway pressure at 36 weeks' postmenstrual age; severe cerebral lesions, defined as intraventricular hemorrhage with ventricular dilation and intraparenchymal hemorrhage; cystic periventricular leukomalacia; and stage II and III necrotizing enterocolitis, according to Bell staging.

### Statistical Analysis

We used a propensity score approach to control for observed confounding factors that might influence both group assignment and outcome.\(^16\) Propensity score was defined as the infants' probability of undergoing early screening echocardiography based on their individual observed covariates. Probability was estimated using a logistic regression model with early screening echocardiography as the dependent variable in relation to the following baseline maternal and infant characteristics (eTable 1 in the Supplement): gestational age, sex, birth weight z score based on Olsen curves,\(^17\) antenatal corticosteroids, main pregnancy complications, inborn status, mode of delivery, Apgar score, intubation at birth, surfactant therapy, respiratory distress syndrome, and early neonatal infections. Given the variation of early screening echocardiography before day 3 of life across
intensive care units (range, 0%-100%), we did not consider the treatment center as a covariate in the propensity score. Instead, we used a proxy for center expertise, defined by summing the number of 24- to 28-week preterm infants spending their first consecutive 48 hours in the center. The proportion of patients with missing data ranged from 0% to 8.5%, exceeding 4% only for Apgar score at 5 minutes. Missing data were treated as a separate category.

The primary analysis was based on propensity matching. We used a 1:1 matching algorithm without replacement to match exposed and nonexposed newborns on gestational age, sex, and propensity score within a caliper of 0.2 standard deviation of the logit of the propensity score. Imbalance after matching was checked. The analysis of the matched set was carried out in 2 steps. First, the timing of ductus arteriosus echocardiographic evaluation, echocardiographic parameters, treatment, and in-hospital mortality were compared between exposed and nonexposed infants. Second, odds ratios (ORs) were calculated to quantify the association between exposed and nonexposed infants. We used neonatal unit preference for early screening echocardiography as a covariate in the propensity score analysis of the principal analysis, since propensity score–based approach was used because of the limited risk of confounding in neonatal units with a homogeneous strategy, which did not depend on the infants’ characteristics. A sixth analysis was performed using data from preterm infants still alive at day 2 (n = 1538) to ensure that early screening echocardiography was not associated with an increase in the early mortality rate.

For analyses performed on the overall cohort, we used weighted percentages and gestational age adjustments in the multivariable analysis to take into account the differences in the recruitment times for the infants born at 24 to 26 weeks of gestation and those born at 27 to 31 weeks of gestation. All tests were 2-sided. P values less than .05 were considered significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc).

Results

Study Population

Among the 1633 extremely preterm infants admitted to NICUs during the study period, 70 died within the first 2 days, leaving 1563 alive at day 3. Among these, information about the timing of the echocardiographic assessment and its indication was available for 1513 infants: 847 underwent early screening echocardiography (exposed group) and 666 did not (nonexposed group) (Figure 1). These infants were hospitalized in 68 NICUs, wherein the percentage of early screening echocardiography varied from 0% to 100%. There was no significant relationship between this percentage and the volume of patients per NICU (Pearson correlation $r = 0.06, P = .63$; eFigure 1 in the Supplement), proportion of inborns ($r = −0.03, P = .84$), and proportion of extremely preterm (<27 weeks of gestation) infants ($r = −0.05, P = .69$) observed among the 61 NICUs with more than 5 infants enrolled. Differences between the exposed and nonexposed infants are presented in Table 1 and in eTable 1 in the Supplement.
Considered, the proportion where received a PDA treatment when
If only infants for whom echocardiography was performed are
\[ ARR \text{ in events per 100 infants, } -12.0 \text{ [95% CI, } -17.3 \text{ to } -6.7 \text{]).}

Ratio \[ OR, \text{ 1.62 [95% CI, 1.31 to 2.00]; absolute risk reduction}
in the exposed group (43.1% vs 55.1%, Pearson \chi^2 test, \text{P}<.001 [Table 1]).

Sensitivity analyses in the overall cohort.

Added Analyses
The negative control analysis did not show any significant
association between early screening echocardiography and
Table 1. Select Baseline Characteristics, Patent Ductus Arteriosus Screening, and Treatment Management According to Exposure to Early Screening Echocardiography for PDA

| Characteristic | Overall Cohort* | | | | Matched Cohort* | | | | Standardized Difference, %b | | | |
|---------------|----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|               | Nonexposed     | Exposed         | Standardized    | Nonexposed     | Exposed         | Standardized    | Nonexposed     | Exposed         | Standardized    | Nonexposed     | Exposed         | Standardized    |
|               | No./Total (%)  | 27.0 (26.0 to 28.0) | 26.0 (25.0 to 28.0) | 20.7 | 27.0 (26.0 to 28.0) | 0 | | | | | | |
|               | Male           | 370/666 (55.4) | 417/847 (49.2) | 12.3 | 330/605 (54.5) | 330/605 (54.5) | 0 | | | | | |
|               | Multiple births| 214/666 (32.1) | 278/847 (32.7) | 1.2 | 197/605 (32.6) | 196/605 (32.4) | 0.4 | | | | | |
|               | Birthweight z score, median (IQR) | 0.00 (−0.66 to 0.55) | 0.07 (−0.71 to 0.63) | 4.7 | 0.04 (−0.65 to 0.58) | 0.04 (0.71 to 0.59) | 2.7 | | | | | |
|               | Antenatal corticosteroids | No | 111/666 (15.9) | 158/847 (18.7) | 7.5 | 106/605 (17.5) | 110/605 (18.2) | 1.7 | | | | |
|               | | Yes | 538/666 (81.6) | 677/847 (79.9) | 4.3 | 487/605 (80.5) | 485/605 (80.2) | 0.8 | | | | |
|               | | Information missing | 17/666 (2.6) | 12/847 (1.4) | 8.1 | 12/605 (2.0) | 10/605 (1.7) | 2.5 | | | | |
|               | Time of first echocardiographic evaluation | No evaluation | 125/666 (19.7) | 0/847 | | 107/605 (17.7) | 0/605 | | | | | |
|               | | Evaluation before day 3 | 108/666 (16.0) | 847/847 (100) | | 103/605 (17.0) | 605/605 (100) | | | | | |
|               | | Evaluation at day 3 or after | 433/666 (64.2) | 0/847 | | 395/605 (65.3) | 0/605 | | | | | |
|               | Observed PDA markers during echocardiographic evaluations | Ductus arteriosus diameter >1.5 mm/kg | 324/541 (59.0) | 540/847 (62.5) | | 309/498 (62.0) | 383/605 (63.3) | | | | | |
|               | | Pulsatile ductus shunt flow pattern | 97/541 (17.6) | 184/847 (21.7) | | 94/498 (18.9) | 134/605 (22.1) | | | | | |
|               | | High-velocity flow in left pulmonary artery | 144/541 (26.5) | 269/847 (30.9) | | 137/498 (27.5) | 186/605 (30.7) | | | | | |
|               | | Diastolic aortic flow reversal or low superior vena cava flow | 57/541 (10.3) | 85/847 (9.7) | | 50/498 (10.0) | 56/605 (9.3) | | | | | |
|               | Treatment of ductus arteriosus | Ibuprofen before day 3 | 44/659 (6.6) | 289/834 (33.9) | | 43/598 (7.2) | 196/595 (32.9) | | | | | |
|               | | Ibuprofen or surgery at day 3 or after | 225/659 (32.9) | 193/834 (22.2) | | 215/598 (36.0) | 132/595 (22.2) | | | | | |
|               | | No treatment | 390/659 (60.5) | 352/834 (43.9) | | 340/598 (56.9) | 267/595 (44.9) | | | | | |
|               | | Information missing | 7 | 13 | | 7 | 10 | | | | | |
| Abbreviations: IQR, interquartile range; PDA, patent ductus arteriosus. | a To take into account any differences in the sampling process between children included at 24 to 26 weeks’ gestation and 27 to 28 weeks’ gestation, percentages are weighted by the gestational age. | b Standardized difference is the mean difference divided by the pooled standard deviation, expressed as a percentage. | c Gestational age was defined as the best obstetric estimate combining last menstrual period and early echography assessment. | d Missing values were considered as marker not observed. |

Figure 2. Multivariable Analysis of In-Hospital Mortality in Preterm Infants Alive at Day 3

Analysis Method | No. of In-Hospital Deaths/No. of Patients (%) | OR (95% CI) | Favors Exposed | Favors Nonexposed
--- | --- | --- | --- | ---
Propensity-matched cohort | 112/605 (18.5) | 86/605 (14.2) | 0.73 (0.54-0.96) | | |
Overall cohort | | | | |
Model | | | | |
1 | 120/666 (18.0) | 136/847 (16.1) | 0.75 (0.57-0.99) | | |
2 | 120/666 (18.0) | 136/847 (16.1) | 0.77 (0.58-1.02) | | |
3 | 120/666 (18.0) | 136/847 (16.1) | 0.74 (0.55-0.98) | | |
4 | 120/666 (18.0) | 136/847 (16.1) | 0.75 (0.55-1.03) | | |
Model 1 adjusted for gestational age; model 2, for gestational age, sex, and birthweight z score; model 3, for gestational age, weighted by the inverse of the propensity score; model 4, for gestational age, weighted by the inverse of the propensity score and with analysis accounting for clustering on neonatal units. The position of each square represents the point estimate of the exposure effect. Error bars indicate 95% confidence intervals.
Table 2. Mortality and Neonatal Morbidity According to Ductus Arteriosus Echocardiographic Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall Cohortᵃ</th>
<th>Matched Cohortᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Total (%)</td>
<td>No./Total (%)</td>
</tr>
<tr>
<td>Death during hospitalization</td>
<td>Nonexposed</td>
<td>Exposed</td>
</tr>
<tr>
<td></td>
<td>120/666 (16.8)</td>
<td>136/847 (15.1)</td>
</tr>
<tr>
<td>Treatment of ductus arteriosus and death during hospitalizationᵇ</td>
<td>9/44 (20.4)</td>
<td>58/289 (19.4)</td>
</tr>
<tr>
<td>Death among preterm infants treated with ibuprofen before day 3</td>
<td>32/225 (13.5)</td>
<td>26/193 (12.5)</td>
</tr>
<tr>
<td>Death among preterm infants treated with ibuprofen or surgery at day 3 or after</td>
<td>77/390 (18.1)</td>
<td>49/352 (12.9)</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>58/656 (8.4)</td>
<td>51/827 (5.7)</td>
</tr>
<tr>
<td>Severe cerebral lesionᶜ</td>
<td>116/655 (16.8)</td>
<td>163/843 (18.2)</td>
</tr>
<tr>
<td>Grade III IVH or IPH</td>
<td>98/655 (13.9)</td>
<td>149/843 (16.5)</td>
</tr>
<tr>
<td>Severe bronchodyplasia³</td>
<td>95/577 (15.6)</td>
<td>124/722 (16.4)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>42/655 (6.4)</td>
<td>41/827 (5.0)</td>
</tr>
</tbody>
</table>

Abbreviations: IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage.
ᵃ To take into account any differences in the sampling process between children included at 24 to 26 weeks’ gestation and 27 to 28 weeks’ gestation, percentages are weighted by the gestational age, and the odds ratios (95% CIs) are adjusted by the gestational age.
ᵇ Information on ductus arteriosus treatment is missing for 20 infants in the overall cohort and 17 infants in the matched cohort.
ᶜ Intraventricular hemorrhage with ventricular dilation (grade III IVH); IPH, defined as a large unilateral parenchymal hyperdensity or large unilateral periventricular leukomalacia, defined as periventricular white matter echolucencies during the ultrasound.
³ Treatment with oxygen for at least 28 days plus a need for oxygen concentration of 30% or greater; receiving mechanical ventilator support; or continuous positive airway pressure at 36 weeks' postmenstrual age.

Figure 3. Cumulative Probability of In-Hospital Death in the Matched Cohort

![Graph showing cumulative probability of in-hospital death](chart.png)

Y-axes shown in blue indicate range from 0% to 20%.

late-onset infection after adjustment for propensity score in the overall cohort (adjusted OR, 1.1 [95% CI, 0.9 to 1.4]). Analysis performed in preterm infants alive at day 2 (eFigure 3 in the Supplement) showed results similar to those of the primary analysis. Among preterm infants alive at day 3 and admitted into the 21 NICUs that performed early screening echocardiography for either more than 85% or less than 15% of their patients, the association was statistically signifcant (adjusted OR, 0.52 [95% CI, 0.31 to 0.86]) (eFigure 4 in the Supplement).

Discussion

In this study, early screening echocardiography was associated with lower rates of in-hospital mortality and pulmonary hemorrhage, a well-recognized life-threatening complication of PDA.³³ The higher mortality in the nonexposed group was mainly observed in untreated infants, who were in higher proportion in that group.

These findings are consistent with previous studies that reported a relationship between PDA and increased mortality in very premature infants.²⁻²⁹,³₀ Animal experiments have shown a causal link between PDA and morbidity.³¹ Our survival curves reveal that the increase in mortality in the nonexposed group occurred at the end of the first postnatal week, consistent with the usual delay observed before PDA becomes clinically symptomatic. Moreover, the decrease in pulmonary hemorrhage rate is in agreement with the results of a recent randomized therapeutic trial based on echocardiographic screening.⁶ Nevertheless, the significant decrease in mortality attributable to pulmonary hemorrhage only partially explains the difference in in-hospital mortality between the 2 groups, since multiple organ failure with or without proven sepsis and respiratory failure also accounted for excessive mortality in the nonexposed group.

Randomized clinical trials are the standard strategy to assess medical interventions. However, neither individual
randomized clinical trials nor meta-analyses have demonstrated any benefit of PDA treatment on survival and long-term outcomes of patients.\textsuperscript{2,3,32,33} Unfortunately, this lack of benefit can be misinterpreted,\textsuperscript{2} because most randomized clinical trials focused on the timing of early treatment, rather than on the risks of PDA closure vs prolonged patentcy. Indeed, open-label rescue treatment was given to 15% to 40% of patients in the placebo groups.\textsuperscript{6,32,33} This backup treatment strategy, which is difficult to control for in randomized clinical trials, may induce biases and hinder any definitive conclusion about PDA treatment.\textsuperscript{3,5}

As in all observational studies, the main limitation of our study is uncontrolled confounding. We used multiple statistical approaches to reduce biases as much as possible. To control for the indication bias inherent in this type of study, we performed a propensity score analysis and made a rigorous adjustment for confounding factors, minimizing the likelihood of incorrectly attributing the association to early echocardiographic screening. At the individual level, performing an echocardiographic evaluation because of clinical signs of PDA, instead of screening echocardiography, classified an infant in the nonexposed group. This could have caused a bias toward classifying the sickest infants in the nonexposed group. Indeed, the presence of PDA in a premature infant is a risk factor for unfavorable outcomes. Nevertheless, the difference in in-hospital mortality between the 2 groups was not apparent in the subgroup of preterm infants who displayed clinical signs of PDA, underwent echocardiography, and were subsequently treated. On the contrary, increased mortality was observed in the infants from the nonexposed group in whom PDA was never assessed or treated. At the NICU level, the complementary analysis of infants hospitalized in the subgroup of neonatal units with a highly consistent screening strategy (either >85% or <15% of patients exposed) confirmed the relationship between early screening echocardiography and decreased mortality. Although the instrumental variable was not statistically significant and thus not completely confirmatory, this analysis provided a point estimate close to that from the primary analysis using propensity score matching and could still be considered supportive because of similar effect size and because the confidence interval just crossed 1. Moreover, we did not observe any relationship between the characteristics of a NICU and its PDA screening strategy, suggesting the lack of performance bias. The reasons for PDA screening seem to be based on medical opinion.\textsuperscript{34}

The strengths of the EPiPAGE 2 study include its population-based cohort design and prospective enrollment of all infants born prematurely in France in 2011. Furthermore, the data on hemodynamic status were prospectively collected with a detailed standardized questionnaire and standardized definitions. Therefore, comprehensive and accurate information was available on our variable of interest. The originality of this study consists in evaluating the association between early screening echocardiography, rather than early treatment, and in-hospital mortality. Neonatologists who favor conservative management of PDA usually do not actively screen infants. Therefore, we chose a marker that would reflect the overall opinion about PDA.

Conclusions

In this national population-based cohort of extremely preterm infants, screening echocardiography for PDA before day 3 of life was associated with lower in-hospital mortality and likelihood of pulmonary hemorrhage but not with differences in necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions. However, results of the instrumental variable analysis leave some ambiguity in the interpretation, and longer-term evaluation is needed to provide clarity.

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