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Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?

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Medical and surgical interventions are widely used to close a persistently patent ductus arteriosus in preterm infants. Objective evidence to support these practices is lacking, causing some to question their usage. Emerging evidence suggests that treatments that close the patent ductus may be detrimental. This review examines the history of and evidence underlying these treatments. Neither individual trials, pooled data from groups of randomized-controlled trials, nor critical examination of the immediate consequences of treatment provide evidence that medical or surgical closure of the ductus is beneficial in preterm infants. These conclusions are supported by sufficient evidence. Neither continued routine use of these treatments nor additional clinical trials using similar designs seems to be justified. A definitive trial, comparing current standard management with novel strategies not primarily intended to achieve ductal closure, may be necessary to resolve doubts regarding the quality or conduct of prior studies. *Journal of Perinatology* (2010) **30,** 241–252; doi:10.1038/jp.2010.3; published online 25 February 2010

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Persistent patency of the ductus arteriosus in preterm infants with respiratory distress syndrome (RDS) has concerned physicians, as this association was first reported by Burnard in 1959.[1] Over the following two decades, the hemodynamic and pulmonary consequences of delayed ductal closure provided a compelling rationale for treatment to close the ductus. In landmark papers, patent ductus arteriosus (PDA) in infants with RDS was linked to bronchopulmonary dysplasia (BPD) by Northway *et al*.,[2] prolonged ventilation by Siassi *et al*.,[3] mortality by Gregory *et al*.,[4] and worsening pulmonary disease by Kitterman *et al.*[5] Subsequent studies confirmed the association of PDA with pulmonary hemorrhage,[6,7] severe RDS,[8,9] BPD,[10–12] necrotizing enterocolitis (NEC),[13,14] renal impairment,[15] intraventricular hemorrhage (IVH),[16,17] periventricular leukomalacia (PVL),[18] cerebral palsy,[19] and death.[20,21] Even now, the adjusted risk of death is increased four-[22] to eightfold[23] for very low birth weight (<1500 g) infants in whom the ductus remains patent after medical therapy.

Controlled and uncontrolled clinical trials showed that surgical ligation[24,25] and indomethacin[26,27] effectively achieve ductal closure. Describing a widespread impression, Kitterman commented.[28]

> 'In [infants] with slight RDS or no lung disease, ligation leads to rapid improvement in cardiorespiratory function and almost all survive. In contrast, when PDA coexists with severe RDS, improvement after ligation is slower and mortality is relatively high due to progressive pulmonary disease and other complications of prematurity.'

The conviction that ductal closure—spontaneous, medical, or surgical—was beneficial became so powerful that the historic National Collaborative Study[29] did not include an untreated or placebo-controlled arm. That trial showed no differences among three treatment strategies in rates of death, BPD, IVH, or NEC; length of hospitalization; outcomes at 1 year; or duration of ventilation or continuous positive airway pressure.[29,30] Monitoring for, diagnosis of, and treatment to eliminate the persistent PDA was nonetheless integrated into neonatal care. Several commentators have suggested that this may not be beneficial.[31–33] Others report that ductal ligation is associated with worse neurodevelopmental outcomes,[34] more severe retinopathy of prematurity (ROP),[34] and increased rates of BPD.[34–36] Uncertainty about current practices prompted this systematic review, with the objective of identifying empirical evidence supporting treatment of persistent PDA in preterm infants.

Findings from individual randomized-controlled trials

Bibliographic searches (PubMed, Web of Science) for 'PDA' or 'persistent ductus arteriosus' restricted to 'human' and 'infant-newborn' produced nearly 4000 citations, almost 1500 relevant to clinical management of PDA in preterm neonates. Reviews and commentaries were numerous, but did not contain citations to

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original evidence of treatment efficacy. Search results and citation lists for prior publications identified 75 randomized-controlled trials of interventions that close a PDA in preterm infants. In 26 trials (five comparing long and short courses of indomethacin,[37–41] 19 comparing indomethacin and ibuprofen,[42–60] and two that included very early crossover to treatment of nonresponders[29,61]), rates of ductal closure did not differ between treatment assignments, precluding evaluation of effects of ductal closure on other outcomes, so these were excluded. The remaining 49 trials,[36,62–109] including 4728 subjects, were deemed potentially informative, as all but one documented substantial reduction in ductal patency after treatment. (The exception was a trial of surgical ligation,[62] for which this difference was assumed.)

Several trials found that fewer treated infants subsequently required ligation, but few other differences in outcomes were shown. Mortality was reduced in only one study (22 subjects).[68] Among 27 studies that reported rates of BPD (using a variety of diagnostic criteria), one found a decrease[78] and two an increase[36,107] among treated infants. None reported reduced oxygen use at 28 days or 36 weeks postmenstrual age (PMA); one found more oxygen use at 36 weeks PMA.[36] Of 25 studies reporting the combined outcome of death or BPD, only one showed a reduction.[78] A single trial of prophylactic ligation described a decrease in NEC,[64] and one trial of ibuprofen prophylaxis found more NEC,[87] but most found no effect. IVH rates were lower in 3 trials of prophylactic indomethacin,[91,96,98] 2 trials reported lower rates of IVH>grade 2,[100,106] and 30 found no effect. A reduction in cerebral palsy in one small (27 subjects) trial of indomethacin prophylaxis[95] was not confirmed in two larger studies.[100,106] No trial showed beneficial impacts on pulmonary hemorrhage,[96,99,102,103,106] severe pulmonary hemorrhage,[110] PVL,[83,84,86–89,95,96,100,101,103,107] any ROP[62,64,72–74,76,84,85,89,90,95,96,105,106] or ROP $\geqslant$ stage 2[84] or stage 3,[89,96,111] Bailey mental developmental index[79,96,106] or psychomotor developmental index,[79,96] mean Wechsler Preschool and Primary Scale of Intelligence, revised scores,[112] severe developmental delay,[96,100,106] or neurosensory impairment or neurosensory impairment or death.[96,103,106] In summary, individual randomized-controlled trials provide scant evidence of benefit from prophylaxis or treatment of PDA in preterm infants.

A few studies have suggested that treatment may be associated with worse outcomes. The National Collaborative Study showed no differences in several primary outcomes (as noted above), but the best outcomes were observed among infants assigned the least intervention (indomethacin only if PDA persisted with usual medical therapy, ligation only as backup).[29] Analysis of data from the Trial of Indomethacin Prophylaxis in Preterms trial suggested that ductal ligation compared with medical therapy alone is associated with more neurosensory impairment, BPD, and severe ROP.[34] Re-examining data from a randomized trial of prophylactic ligation,[64] Clyman *et al*.[36] found that ligation increased the likelihood of requiring oxygen at 36 weeks PMA. In a retrospective regression analysis of factors associated with morbidity in infants treated for PDA, Chorne *et al*.[35] found that chronic lung disease (oxygen use at 36 weeks PMA) is associated with ductal ligation, but not with use of >3 indomethacin doses, persistent PDA after indomethacin prophylaxis, or symptomatic PDA. More is not better: early indomethacin is worse than later indomethacin[29] and ligation is worse than either medical therapy[29,34,35] or no treatment.[36]

Pooled results from randomized-controlled trials

These trials have been the subject of several Cochrane reviews,[113–118] which have found no evidence for long-term benefits of treatment to close the ductus. As the purpose of Cochrane reviews is identification of strong evidence in support of an intervention, many trials were excluded from meta-analyses because of methodological deficiencies. The objective of this systematic review is to ascertain whether there is *any* evidence, however weak, to support these measures, so no trials were eliminated from further consideration because of such concerns. To determine whether failure to identify effects on outcomes reflected the lack of statistical power in individual trials, data from randomized-controlled trials[36,62–109] were pooled, and point estimates and confidence intervals (CIs) for pooled odds ratios (ORs) were calculated by the method of Mantel and Haenszel.[119] The results for treatment trials, for which enrollment criteria included the presence of a symptomatic or asymptomatic patent ductus, are shown in Figure 1. The results for prophylaxis trials, in which infants were enrolled before expected ductal closure, are shown in Figure 2. Figure 3 represents the results for pooled data for all treatment trials (panel a), all prophylaxis trials (panel b), or all trials (panel c). All interventions are quite effective for closing the ductus (OR and CIs at the top of each panel in Figures 1–3). If the benefits of treatment are mediated by closure of the ductus, it should not matter how that is achieved, so pooling of these data is appropriate.

Very few outcomes are significantly affected by these interventions. Early trials of oral indomethacin for symptomatic PDA suggested reduced mortality (Figure 1b), but this was not reproduced in trials using intravenous administration (Figure 1d) or when results for both routes were combined (Figure 1e). Indomethacin *treatment* for PDA may increase the risk of IVH (Figure 1f), but indomethacin *prophylaxis* reduced IVH, IVH>grade 2, and PVL (Figures 2d and e). Prophylactic ligation reduced the rate of NEC,[64] but increased BPD[36] (Figure 2a). Pooling data for prophylaxis trials using oral or intravenous indomethacin (Figure 2e), indomethacin or ibuprofen (Figure 2f), or medical or surgical prophylaxis (Figure 3b) did not change those conclusions, except that the apparent reduction in PVL was

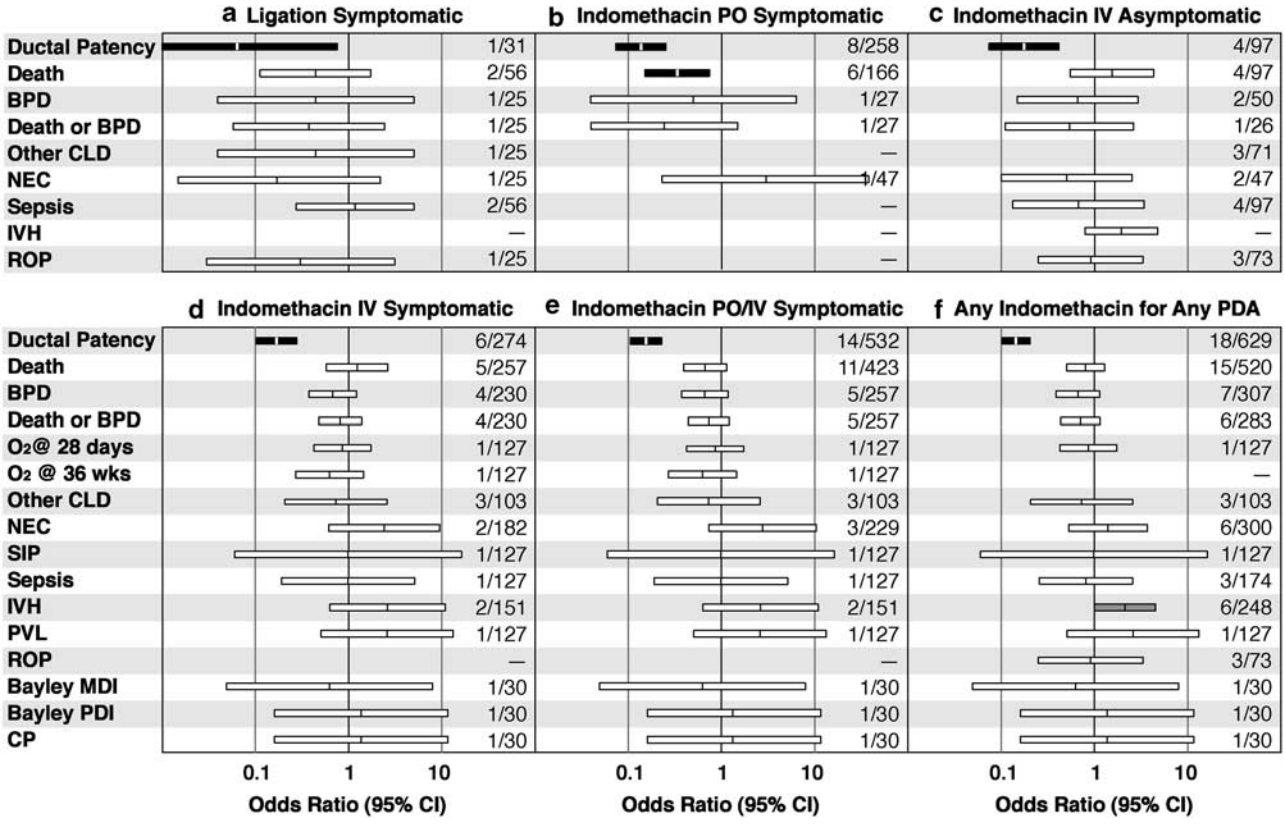

Figure 1 Pooled results of randomized-controlled trials of treatment of persistently patent ductus arteriosus in preterm infants. Each panel is titled with the intervention (ligation or indomethacin), route (oral, PO; or intravenous, IV) and indication (symptomatic, asymptomatic, or any PDA). Results are shown for ligation of symptomatic PDA (**a**), oral indomethacin treatment of symptomatic PDA (**b**), intravenous indomethacin treatment of asymptomatic PDA (**c**), intravenous indomethacin treatment of symptomatic PDA (**d**), oral or intravenous indomethacin treatment of symptomatic PDA (**e**), or any indomethacin treatment of any PDA (**f**). Bars represent the 95% confidence limits for each of the outcomes listed at the left; the line at the midpoint of each bar denotes the point estimate of the odds ratio. Bars for OR significantly different from 1 are black (two-tailed $P<0.05$) and or gray (one-tailed $P<0.05$). The number of trials (N) and subjects (n) included for each outcome are listed on the right side of each panel (N/n). BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; MDI, Mental Development Index; PDI, Psychomotor Development Index; CP, cerebral palsy.

no longer significant. A few analyses showed (two-tailed $P<0.05$) an increase in sepsis after ibuprofen prophylaxis (Figure 2c) and of chronic lung disease (using nonstandard criteria) after IV indomethacin prophylaxis (Figure 2d), or suggested (one-tailed $P<0.05$) increased spontaneous intestinal perforation with intravenous ibuprofen prophylaxis (Figure 2c) and more severe ($\geqslant$stage III) ROP with intravenous indomethacin prophylaxis (Figure 2d). Pooled data from all trials (Figure 3c) identified only two significant effects of treatment to induce ductal closure: reduction in ductal patency itself and in IVH>grade 2. In summary, no matter how the trials are grouped, or how rigorous (Cochrane analyses) or permissive (these analyses) the inclusion criteria, the pooled data show that treatments are effective in achieving the primary objective of therapy—ductal closure (OR: 0.23, 95% CI: 0.20–0.26)—but, with a single exception, fail to improve other reported outcomes. CIs for these effect estimates are quite narrow, particularly for those of greatest interest (death, death or BPD, BPD, oxygen use at 28 days or 36 weeks, NEC, IVH, ROP, developmental delay, cerebral palsy, and neurosensory impairment), so it is unlikely that an undetected benefit will become evident through enrollment of infants in additional similar clinical trials.

Reduced rates of IVH and IVH>grade 2 with indomethacin prophylaxis were apparent (Figures 4a and b) even before publication of trials adequately powered to independently detect them,[100,106,112] and so are not attributable to just one or two trials with anomalous results. The relationships between IVH, PDA, treatments, and outcomes remain ambiguous, however. Indomethacin *treatment* of PDA (Figure 4c) is associated with a greater overall rate of IVH (one-tailed $P<0.05$; rates of IVH>grade 2 were not reported). In separate trials, mortality[97] and IVH[107] rates were *greater* among infants <1000 g who received indomethacin prophylaxis. Ment *et al*.[91,98] found that prophylactic indomethacin was associated with the reduction in both IVH and PDA, but these effects were independent, and PDA closure did not affect progression of IVH to parenchymal involvement.[101] Their large multicenter trial showed both ductal closure and reduced IVH>grade 2,[100] but long-term follow-up revealed few

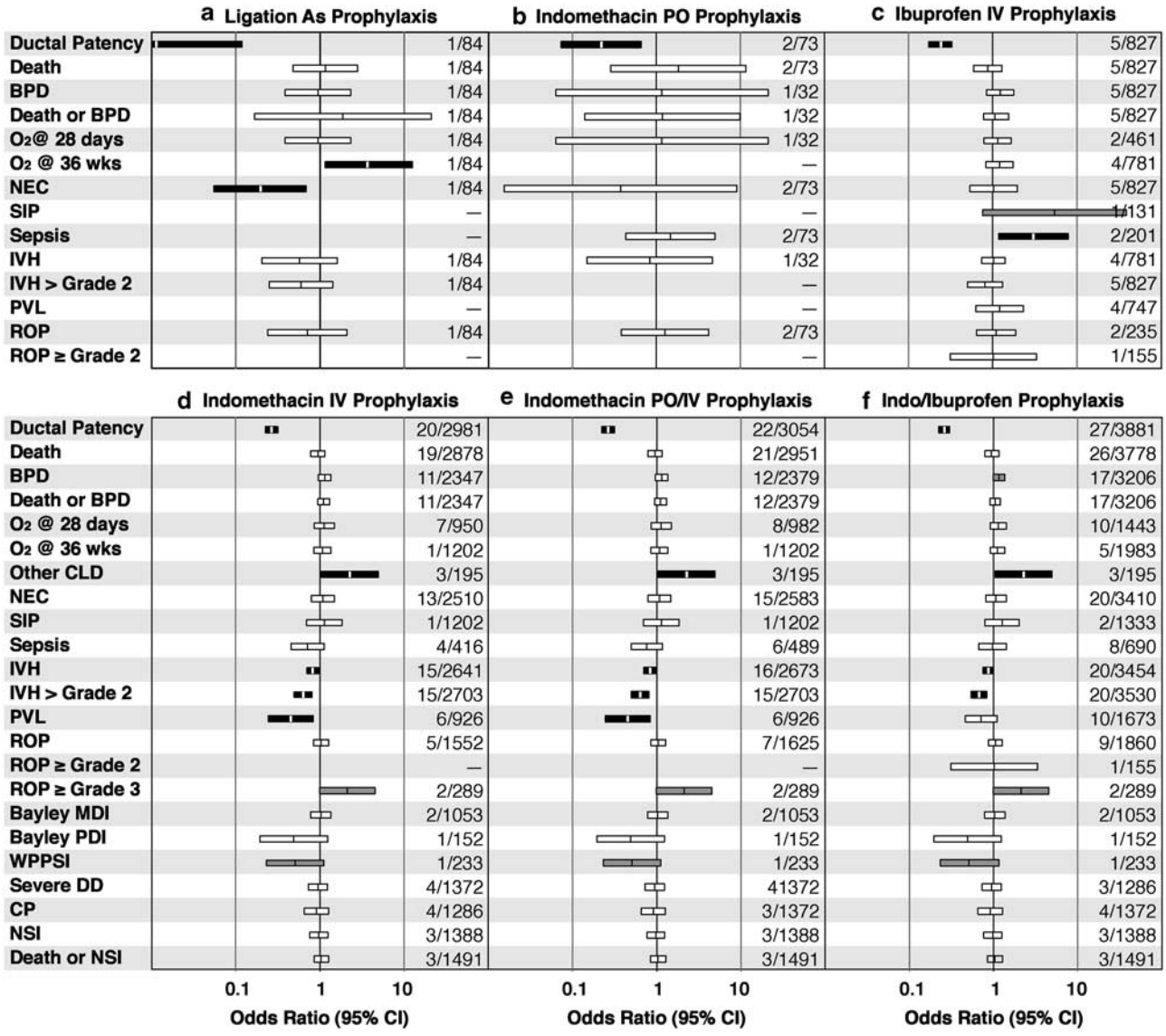

Figure 2 Pooled results of randomized-controlled trials of prophylaxis for persistently patent ductus arteriosus in preterm infants. Each panel is titled with the intervention (ligation, indomethacin, or ibuprofen) and route (oral, PO; or intravenous, IV). Results are shown for prophylactic PDA closure using ligation (**a**), oral indomethacin (**b**), intravenous ibuprofen (**c**), intravenous indomethacin (**d**), oral or intravenous indomethacin (**e**), and either indomethacin or ibuprofen (**f**). Symbols and abbreviations are as indicated for Figure 1. WPPSI, Wechsler Preschool and Primary Scale of Intelligence; DD, developmental delay; NSI, neurosensory impairment.

neurodevelopmental differences;[112] indomethacin prophylaxis recipients were less likely to score <70 on the full-scale Wechsler Preschool and Primary Scale of Intelligence, revised (9 vs 17%; $P = 0.035$) or Peabody Picture Vocabulary Test–revised (12 vs 26%; $P = 0.02$), but there were no differences in their mean performance, verbal, or full-scale IQ scores, Peabody Picture Vocabulary Test–revised scores, or rates of cerebral palsy, seizures, or neurosensory impairment. The Trial of Indomethacin Prophylaxis in Preterms trial found no improvement in rates of death, neurosensory impairment, or both in association with indomethacin prophylaxis.[106] These results reflect the apparently modest and independent functions of PDA and IVH in the multifactorial causation of neurodevelopmental deficits in the context of current practices. They do not support the hypothesis that prevention or treatment of a persistent PDA improves neurodevelopmental outcome.

Explaining the missing benefits

Clyman[120] has suggested that beneficial effects might become apparent in pooled data from studies grouped on the basis of timing of treatment assignments (Figure 5) or of rescue treatment in the control groups (Figure 6a).[121] Benefits also might be apparent only in studies conducted after the advent of exogenous surfactant therapy (17 trials since 1989; Figure 6b), or in those that enrolled more immature infants (19 trials with mean

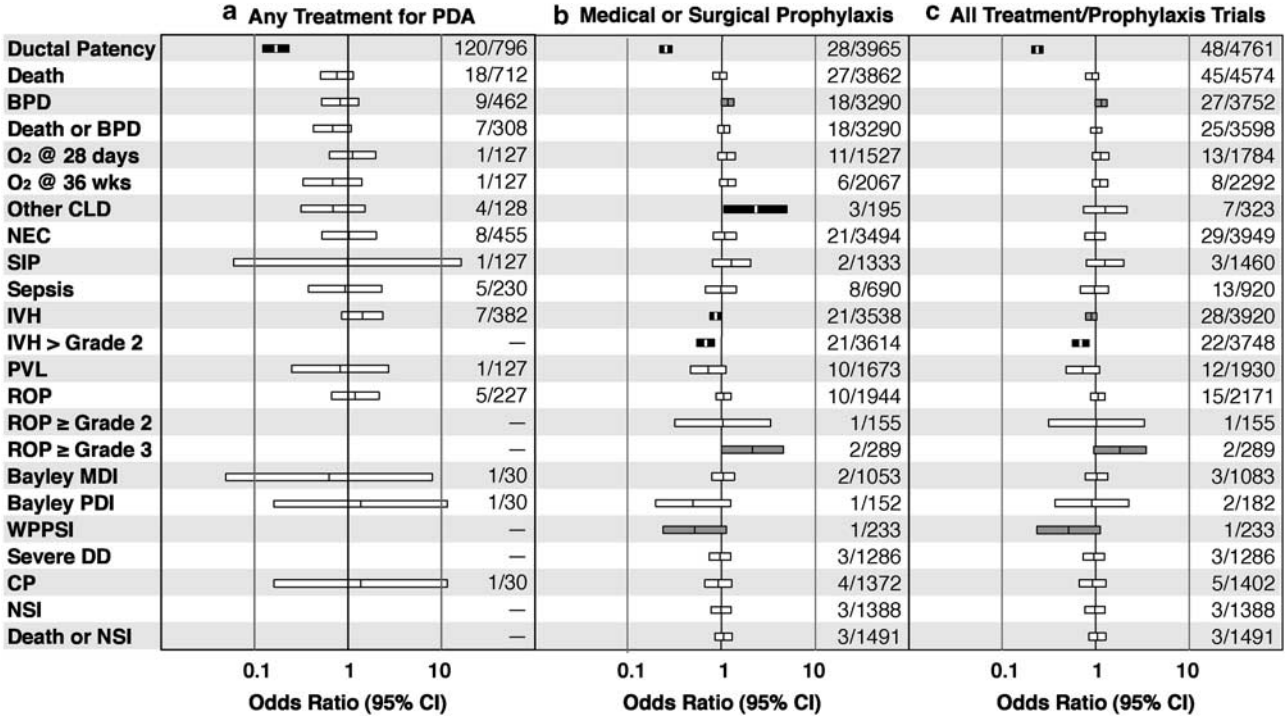

Figure 3 Pooled results of randomized-controlled trials of treatment (**a**), prophylaxis (**b**), or either intervention (**c**) for persistently patent ductus arteriosus in preterm infants. Symbols and abbreviations are as indicated for Figures 1 and 2.

gestational age <29 weeks; Figure 6c). Three small trials comparing early and late treatment suggested reduced rates of chronic lung disease (diagnosed using unspecified[70] or radiographic[76,78] criteria) or the combined outcome of death or chronic lung disease (Figure 5c), but no other earlier unrecognized benefits are apparent in data pooled using these strategies (Figures 5 and 6).

Obscuration of benefits by crossover of control subjects to open treatment has been proposed as an explanation for the absence of demonstrable benefit.[121,122] Crossover of control subjects would reduce the magnitude of any differences, but should not completely eliminate them. When few subjects have been studied and CIs for the ORs for effects of interest are correspondingly wide (for example Figure 1a), low signal-to-noise ratios predispose to such type II errors. With larger sample sizes, narrow CIs (for example Figure 3c) make it much less likely that an effect will be missed because of an artifactual reduction in its apparent magnitude. Production of an observed lack of effect such as that shown for death or BPD in all trials (OR: 1.01, 95% CI: 0.88–1.12) would require a very small 'true' magnitude of the effect, or crossover of nearly all control subjects along with negligible detrimental effects of delaying treatment; neither instance suggests benefit from inducing ductal closure. In brief, it is logically inconsistent to suppose that effects of crossover to treatment are sufficient to completely obscure substantial effects on outcomes such as BPD, but insufficient to reduce the consistent, large, and statistically robust effect on rates of ductal patency. If crossover to open treatment after some delay does account for the lack of treatment effect, it would provide evidence that there is no, or at most a very small, detrimental effect of prolongation of ductal patency during that interval.

Effects of induced ductal closure on pulmonary function

Although observations of rapid improvement in infants with severe RDS after treatment with indomethacin or ductal ligation suggested that closing the ductus might ameliorate RDS, making management easier or less invasive (even if it does not affect long-term outcomes), there is little evidence to support that hypothesis. The duration of positive pressure ventilation or oxygen supplementation is reported for 28 of the 49 randomized-controlled trials.[62,64,68,70,73–78,83–88,90,92–97,99,103,104] Of these, only five, including a total of 113 subjects, report a shorter duration of oxygen,[70,74] ventilation,[62,77] or both.[68] The reduction in duration of oxygen use among infants with birth weights <1000 g reported by Mahony[74] was not replicated in the National Collaborative Study.[29] Yanagi *et al*.[68] cautioned that reduced duration of oxygen use and ventilation in their trial might be an artifact of significantly greater weight and maturity of indomethacin-treated infants. In two small trials, Cotton *et al*.[62,77] reported shorter duration of ventilation. All of these observations date from 1983 or earlier, so may not be applicable in the post-surfactant era. The other 23 trials reporting

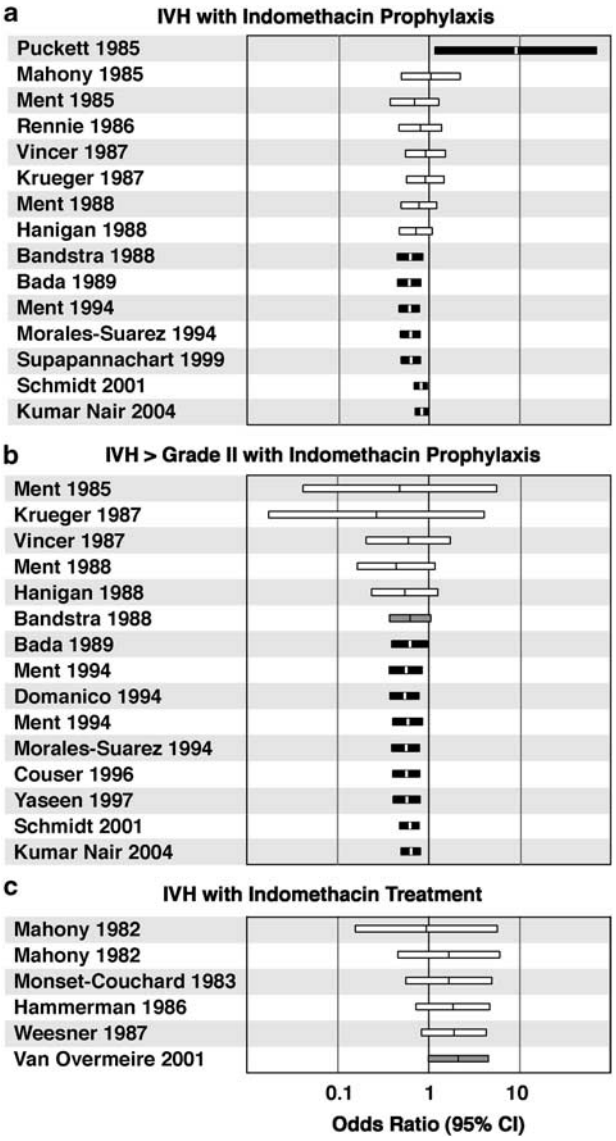

Figure 4 Tornado diagrams for sequentially pooled odds ratios for intraventricular hemorrhage. IVH (**a** and **c**) or IVH>grade 2 in association with indomethacin prophylaxis (**a** and **b**) or indomethacin treatment (**c**) of PDA. Symbols are as indicated for Figure 1.

these endpoints, including 2002 subjects, failed to show reduction in either oxygen or ventilator use; one described prolongation of ventilation in the treatment group.[95] In the sole trial comparing ligation with nonintervention, Cassady *et al*.[64] noted that infants who underwent ligation required longer ventilation (18 vs 12 days), supplemental oxygen (34 vs 24 days), and hospitalization (51 vs 43 days) than control subjects. Those differences were not statistically significant, but more surgically treated babies required ventilation for >45 days[64] and more required oxygen or mechanical ventilation at 36 weeks PMA.[36] Closing the ductus does not shorten the duration of respiratory support required by preterm infants.

Requirements for respiratory support could be more moderate, if not of shorter duration, after treatment to close the PDA. In a randomized-controlled trial of early prophylactic indomethacin, indomethacin-treated infants required significantly more oxygen, had larger alveolar-arterial oxygen gradients, and needed more doses of surfactant.[104] In the Trial of Indomethacin Prophylaxis in Preterms,[123] infants given prophylactic indomethacin required more oxygen on days 3 through day 7 (Figure 7a). In a third trial, earlier use of indomethacin (day 3 vs day 7) in infants <28 weeks gestation was associated with higher oxygen (Figure 7b) and mean airway pressure (Figure 7c) requirements.[83] Thus, early medical closure of the ductus is associated with increased, rather than reduced, respiratory support in the immediate post-treatment period.

Natural history of ductal closure in preterm infants

Early descriptions of the natural history of ductal closure in preterm infants indicated that the ductus almost always closes spontaneously if left alone. In 1963, Powell[124] noted spontaneous closure of persistent PDA in five of six preterm infants. In 1966, Auld[125] described spontaneous delayed closure in seven of seven preterm infants who had PDA at 1 week of age, and Danilowicz *et al*.[126] reported five additional cases of delayed spontaneous closure. The latter authors commented

> '[D]uctal closure in the premature infant may occur up to 4–6 months of age. Although further observations are necessary, at present it would seem justifiable to allow a period up to 6 months after birth for spontaneous closure to occur, before contemplating surgery, unless more urgent indications for operation exist.'

By the early 1970s, Hallidie-Smith[127] and Clarkson and Orgill[128] had added spontaneous ductal closure in 47 of 52 and 18 of 19 preterm infants by 6 months of age, respectively. Siassi *et al*.[129] documented spontaneous closure by an average of 3.1 months of age in 15 of 19 infants with birth weights <2500 g who were followed to age 8 months. As development of techniques for surgical ligation and the availability of indomethacin in the late 1970s were quickly followed by wide adoption of active management of the persistent PDA, little information about the natural history of ductal closure in extremely low birth weight (<1000 g) preterm infants—the most likely candidates for treatment now—has become available over the ensuing three decades.

Such data are beginning to emerge. Spontaneous ductal closure occurred between day 3 and day 7 in 28 of 63 (44%) infants <32 weeks gestation enrolled in a trial of early vs late indomethacin treatment.[83] Among 122 infants with birth weights <1000 g, the ductus closed during the first 3 days after birth in 25, by day 8 in 42, and before discharge in 46.[130] Spontaneous ductal closure was documented in 24% (8 of 34) of infants of

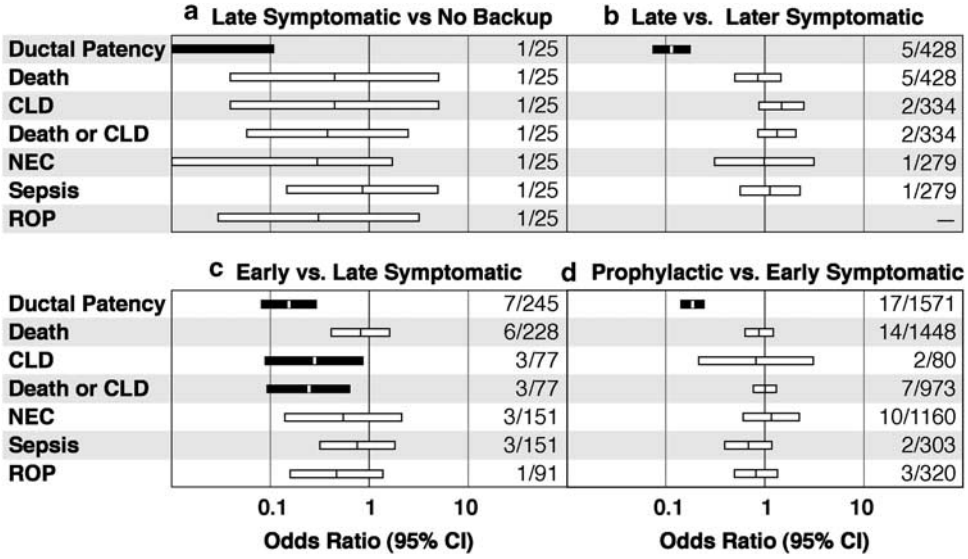

Figure 5 Pooled results of randomized-controlled trials grouped according to the classification of Clyman.[120] Results are shown for lcomparisons of late treatment versus no backup treatment for symptomatic PDA (**a**), late versus later treatment of symptomatic PDA (**b**), early versus late treatment of symptomatic PDA (**c**), and prophylactic versus early symptomatic treatment (**d**). Symbols and abbreviations are as indicated for Figure 1. The results for outcomes not shown were not statistically significant.

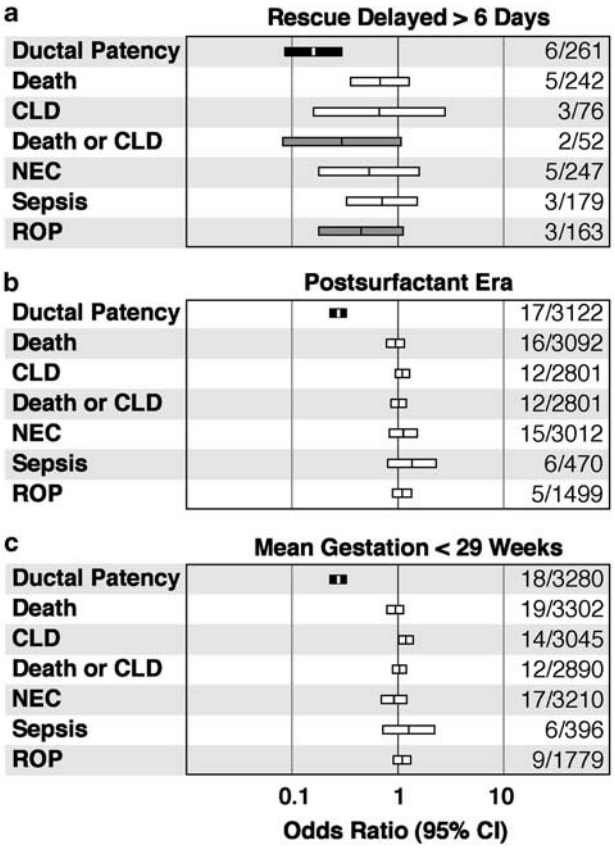

Figure 6 Pooled results of randomized-controlled trials for which intervention in the control group was delayed at least 6 days[121] (**a**), performed since 1989 (**b**), and for which the mean gestational age was <29 weeks (**c**). Symbols and abbreviations are as indicated for Figure 1. The results for outcomes not shown were not statistically significant.

gestational age 23–27 weeks.[131] Spontaneous closure rates, particularly after 7 days of age, may be underestimated, as the majority of infants included in these reports were treated by the second week after birth. In a prospective observational study of 65 very low birth weight (<1500 g) infants, Nemerofsky *et al*.[132] found spontaneous ductal closure by 7 days of age in 31% of those with birth weights ⩽1000 g and in 67% of those with birth weights >1000 g. For those with BW⩽1000 g, spontaneous closure without intervention occurred before discharge in 47% (at a median age of 56 days); one infant was treated with indomethacin in the first week and the remaining 16 had treatment initiated at a median age of 14 days. Among the larger infants (BW>1000 g), no intervention was required in 97% and the ductus spontaneously closed before discharge in 94% (at a median age of 7 days). Another recent observational study[133] showed spontaneous closure of PDA in 100% of 32 very low birth weight (<1500 g) infants who were not treated (66% before and 34% after discharge from the hospital). Among 63 treated infants (7 primary ligation, 56 indomethacin), the ductus closed after primary treatment in 38 (60%); ligation was performed after indomethacin in 15, and 10 were discharged with PDA. In the latter group, 3 infants had persistent PDA at 12 or more months of age. Of 21 infants with PDA at discharge, none experienced a PDA-related morbidity and none died before 18 months. Although these observational data do not prove that treatment for PDA is never necessary (as some infants were treated in each cohort), they indicate that most infants with persistent PDA beyond the third day after birth—particularly those with birth weight >1000 g—can be expected to do well without treatment specifically intended to achieve ductal closure.

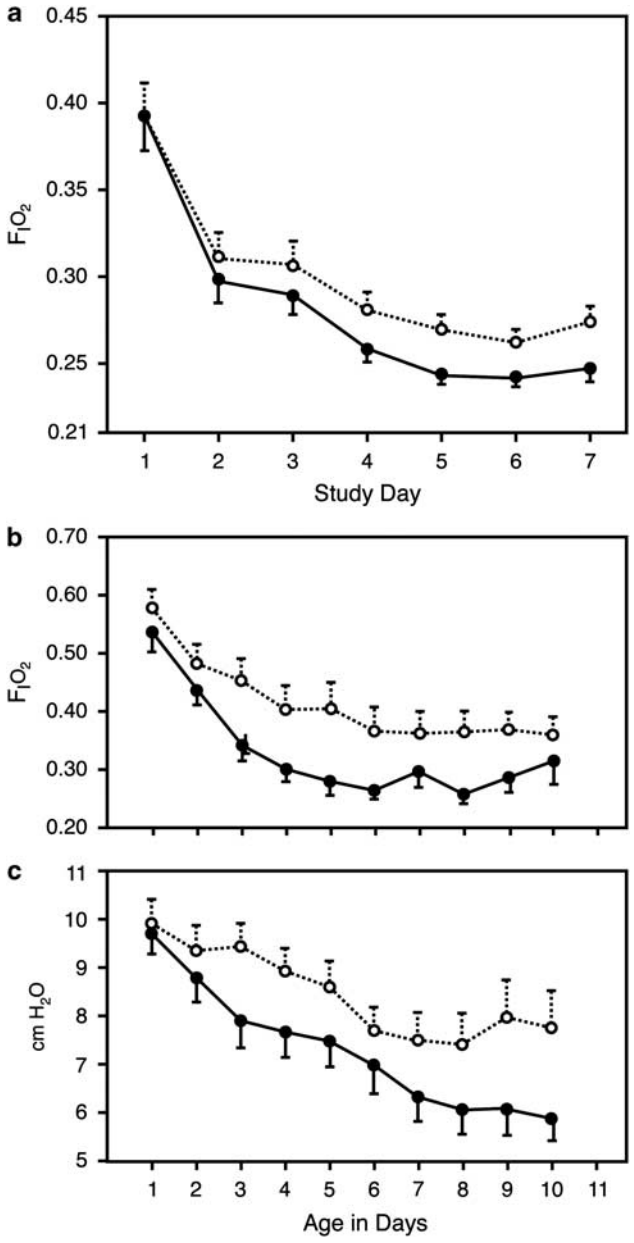

Figure 7 Effects of early indomethacin on requirements for respiratory support. (**a**) Data from the Trial of Indomethacin Prophylaxis in Preterms trial.[123] (Copyright 2006, with permission from Elsevier). The daily mean fraction of supplemental oxygen is plotted with 95% confidence intervals during the first week of life for 999 extremely low birth weight (<1000 g) infants who were randomized to prophylactic indomethacin ($n = 496$) or placebo ($n = 503$) soon after birth and who survived to post-menstrual age 36 weeks. (**b** and **c**) Data from Van Overmeire *et al*.[83] (Copyright 2001, with permission from Elsevier.). Supplemental oxygen requirement (**b**) and mean airway pressure (**c**) in infants with gestational age <28 weeks treated with early (day 3; $n = 23$) or late indomethacin (day 7; $n = 21$). Data points represent means ± s.e. Differences between groups are significant ($P<0.05$) after day 3 (inclusive) in all three panels. Open symbols and dashed lines represent the early indomethacin groups, filled symbols and solid lines represent placebo (**a**) or late indomethacin (**b** and **c**) groups.

Conclusions

Fifty years after Burnard,[1] 49 controlled trials involving nearly 5000 infants address the matter of treatment to close a persistent PDA in preterm infants, yet there is no evidence that this widespread practice benefits its recipients. Absence of evidence of benefit is not an artifact of lack of trials, inadequate statistical power, or noncompliance with trial design. On the contrary, the available evidence indicates that later treatment of fewer infants produces better outcomes. The available data are sufficient to allow, but do not support, rejection of the null hypothesis, despite consistent achievement of the primary objective: earlier closure of the ductus. The time has come to *accept* the null hypothesis: treatments that close the persistent PDA in preterm infants do not improve long-term outcomes. This conclusion has two important implications. First, it is now appropriate to institute a moratorium on routine, early interventions designed to close the ductus in preterm infants. Second, calls for further clinical trials using similar designs should be met with skepticism. Imperfect though they may be, those trials have been performed and the answer is known. The narrow CIs for the most important long-term outcomes (Figure 3c) leave little room for equipoise about the expected outcome.

It would be unrealistic to assume that a practice so deeply ingrained in the culture of neonatal medicine will be readily or quickly abandoned. Pragmatism dictates incremental movement in that direction. Nemerofsky *et al*.[132] have suggested an excellent initial strategy: refrain from treatment altogether in infants with birth weights >1000 g and defer treatment until at least the second week after birth in smaller infants. The available evidence indicates that this will substantially reduce the number of infants subjected to potential adverse effects of treatment without incurring an incremental risk of untoward long-term outcomes.

Failure of multiple trials to show long-term benefits from acceleration of ductal closure implies that the several adverse outcomes that are strongly associated with persistent PDA—severe RDS, BPD, NEC, IVH, PVL, death, etc.—may be linked to PDA through prematurity itself or through some other common antecedent, such as intrauterine infection or inflammation.[75,134] If so, closing the ductus cannot be expected to alter the ultimate outcomes of these otherwise unrelated processes.[135] The research agenda should prioritize a search for the identity of and methods for modification of these antecedent or intermediary processes, to develop tools for preventing these adverse outcomes (and, perhaps, persistent PDA, as well).

The experience that some infants with persistent PDA develop intractable congestive heart failure, respiratory failure from pulmonary overcirculation and edema, and/or signs of other organ ischemia associated with a ductal steal is nearly universal. At least some seem to improve rapidly after interventions that produce ductal closure. This should prompt continued development and evaluation of objective measures of the hemodynamic

consequences of ductal patency, such as the clinical and echocardiographic staging system proposed by McNamara and Sehgal.[136] New technologies that enable direct measurement of tissue perfusion or oxygenation also may prove valuable. Such measures may identify particular subgroups of infants at special risk for adverse outcomes. Randomized intervention trials to test the hypothesis such infants may benefit from ductal closure—even though most infants of comparable weight or gestational age do not—will still be essential.

This should not be mistaken for a call to simply ignore a large left-to-right ductal shunt or its hemodynamic consequences. This disordered physiology requires management to minimize sequelae of systemic underperfusion (renal ischemia, bowel infarction, PVL, and the like) as well as pulmonary overcirculation and edema (aggravating respiratory failure). Management might follow strategies applied in infants with left-to-right shunts associated with congenital cardiac malformations,[137] such as judicious fluid restriction and diuretics for congestive heart failure; use of minimal supplemental oxygen, permissive hypercapnia, and avoidance or correction of metabolic alkalosis to minimize pulmonary vasodilation; application of continuous distending airway pressure to reduce pulmonary blood flow and increase systemic perfusion; and red blood cell transfusion to increase the ratio of pulmonary to systemic vascular resistance[138] and reduce both systemic and pulmonary blood flow.

Some may remain unconvinced that the available data are sufficient for rejection of the null hypothesis, on the grounds that the studies are too old, too severely compromised by crossover to treatment among control subjects, or invalid for other reasons. Another clinical trial may be necessary to resolve those doubts. Such a trial should focus on infants of birth weight $\leqslant 1000$ g who have persistent patency of the ductus >3 days after birth, as that population includes the smallest proportion of infants for whom early spontaneous ductal closure is expected. Limiting enrollment to infants with echocardiographic or tissue perfusion evidence of a hemodynamically significant left-to-right shunt might reduce the sample size required (if these findings correlate with an increased prevalence of adverse long-term outcomes), but would risk delaying initiation of study interventions until after the opportunity to avert adverse outcomes has passed.[121] Its design must not presuppose that induction of ductal closure is useful or necessary. As early treatment to induce closure of a patent ductus is a currently accepted strategy that seems to produce outcomes no worse than observation and delayed treatment, that should be the basis for one treatment arm. Without this, it will be impossible to determine whether the alternative is superior or inferior to induction of ductal closure. The alternative treatment arm must incorporate specific active management strategies, such as those suggested in the preceding paragraph, and provide for abstinence from intervention to actively close the ductus, so that there is a substantial difference in the ages at which ductal closure is achieved in the two treatment groups. No trial can succeed unless those of us who enroll patients are able to refrain from open treatment of ductal patency outside the study protocols. Achievement of this level of equipoise promises to be difficult, both for those who believe and those who doubt that these interventions are beneficial.

Conflict of interest

The author declares no conflict of interest.

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