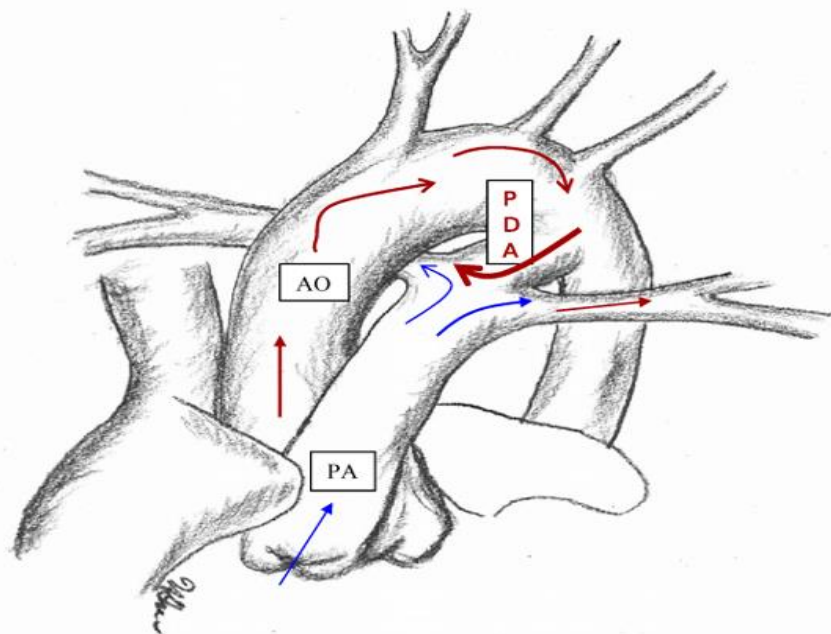


Controversies in the Management of a Patent Ductus Arteriosus

Is there any Benefit to Closing the Ductus Arteriosus?



PDA

Richard A. Polin M.D.

Morgan Stanley Children's
Hospital Columbia University



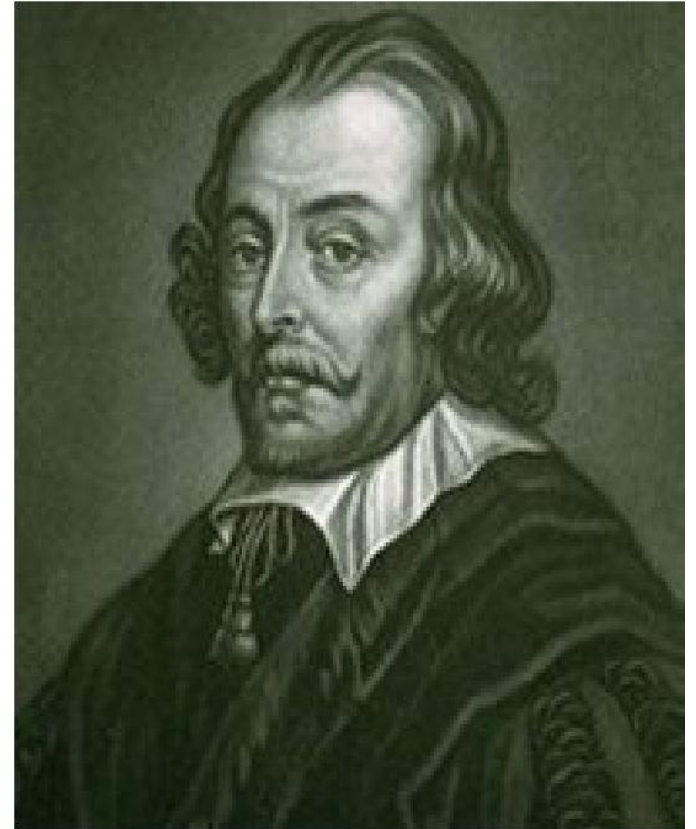


Galen 130-200 AD

“The lung of the fetus does not require the same arrangements of a perfected lung endowed with motion. Nature has therefore anastomosed the pulmonary artery with the aorta.....

“Exercitatio anatomica de motu
cordis et sanguinis in animalibus”

*“The canal shrinks after birth and
after time becomes withered.”*



William Harvey
1558-1657

Surgical ligation of a Patent Ductus Arteriosus: Report of a first successful case. JAMA 112: 729, 1938



Lorraine Sweeney



Robert E. Gross M.D.

Surgical ligation of a Patent Ductus Arteriosus: Report of a first successful case. JAMA 112: 729, 1938



Lorraine Sweeney

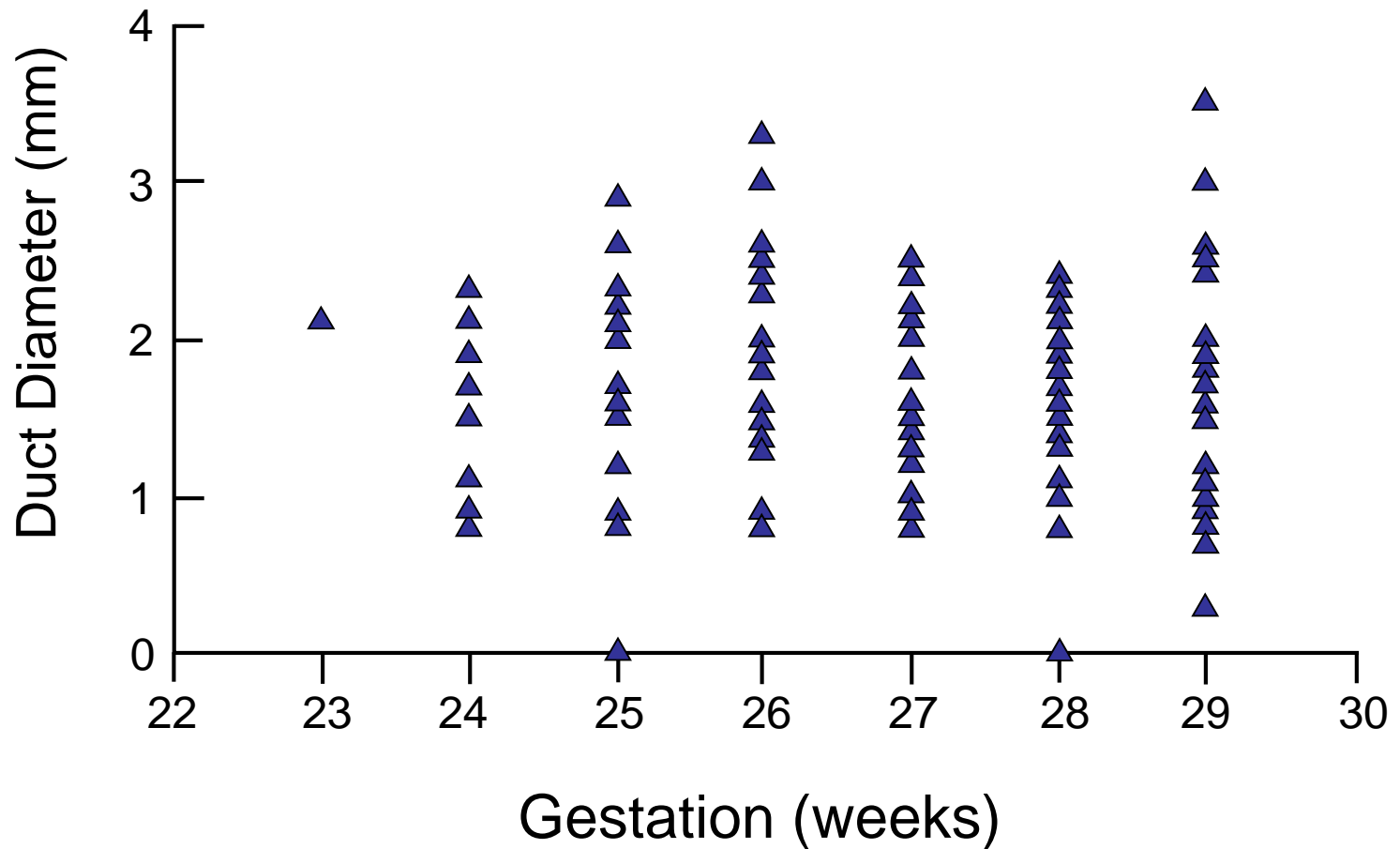
Outline

- ★ Perinatal variables affecting patency of the ductus arteriosus
- ★ Rationale for the medical or surgical closure of a patent ductus arteriosus
- ★ Risks and benefits of indomethacin, ibuprofen and surgery for closure of a PDA.
- ★ Pros and cons of paracetamol for ductal closure
- ★ Recommendations

Perinatal Variables Affecting PDA Incidence?

- | | |
|-------------------------------|----------------------|
| ✓ Premature Delivery | Increase |
| ✓ Antenatal Steroids | Decrease |
| ✓ Antenatal magnesium sulfate | Increase |
| ✓ Antenatal indomethacin | Increase / no effect |
| ✓ Chorioamnionitis | Increase |

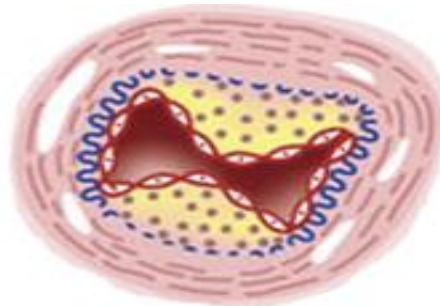
Prematurity & Ductal Size



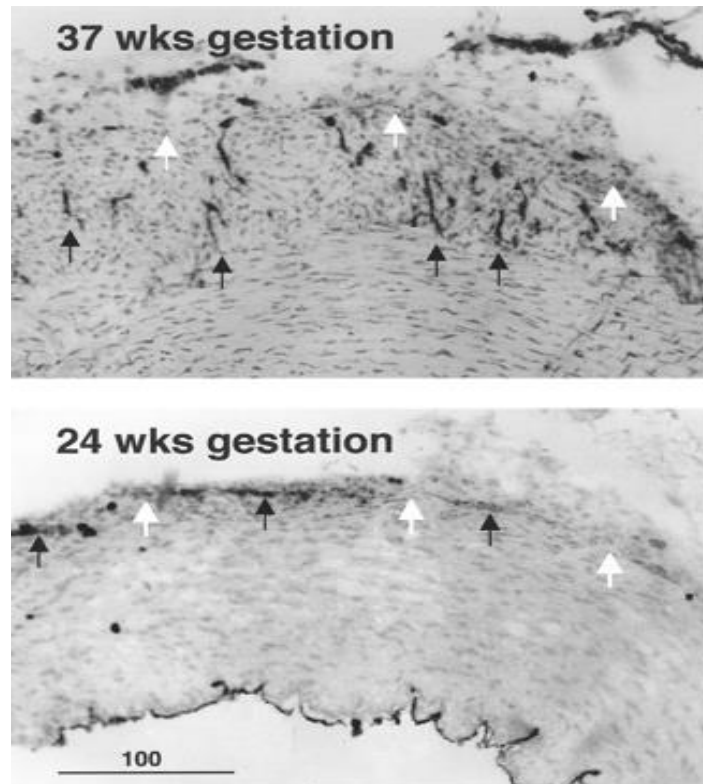
Range of ductal constriction at 5 hours ($n = 124 < 30$ weeks).

Antenatal Indomethacin & PDA

- ★ Indomethacin functions as a tocolytic by inhibiting prostaglandin synthesis leading to ductal constriction.
- ★ Increased risk of PPHN
- ★ Ischemic intestinal injury
- ★ *Increased risk of ductal injury and failed postnatal closure.* In utero ductal constriction decreases blood flow through the vasa vasorum (and increases medial thickness) leading to death of smooth muscle cells (affecting postnatal closure).



Antenatal Indomethacin & PDA



Goldbarg et al Am. J Physiol. 282: 184, 2002

Antenatal Indomethacin & PDA

- ★ Vasa vasorum develop \geq 28 weeks gestation
- ★ Before that time luminal blood flow is sufficient to meet oxygen & metabolic demands
- ★ Thus infants $<$ 28 weeks gestation are less likely to be affected by antenatal indomethacin

Goldbarg SH et al Am. J. Physiol 282: R184, 2002

s Does the Presence of a Patent Ductus Arteriosus in a Preterm Infant Increase Morbidity and Mortality or is it merely associated with Increased Morbidity & Mortality?

What are the Morbidities Associated with PDA?

- ★ IVH/PVH
- ★ Pulmonary hemorrhage/edema
- ★ NEC?
- ★ BPD?
- ★ PVL?
- ★ Early Postnatal hypotension?

Treatment Strategies & Morbidity

	Pulmonary Morbidity	IVH	NEC
Prophylactic v. Early symptomatic	—	↓	—
Early symptomatic v. Late symptomatic	↓	—	↓

Early symptomatic: Days 2-3, Late symptomatic Days 7-8
(CHF)

*What is the effect of the PDA on lung structure
and cardiopulmonary function?*

It depends how long the ductus arteriosus been present?

Pulmonary Mechanics & PDA

- ★ PDA increases fluid and protein movement from the pulmonary vasculature into the lung's interstitium.
- ★ However, an increase in pulmonary lymph flow compensates by clearing the pulmonary interstitium of protein and fluid.

Pulmonary Mechanics & PDA

- ★ Early treatment of PDA has little or no effects on pulmonary mechanics*.
- ★ Early treatment (first 24 hours of life) increases the success of PDA closure (85% vs. 48% after 72 hours) and decreases the risk of subsequent ductal ligation.

* Krauss AN Am J Dis child 143: 78, 1989 & Farstad et al Eur. J Pediatr 153: 903, 1994

Prevention of Bronchopulmonary Dysplasia

The TIPP Trial

- ★ Prophylactic indomethacin decreased the incidence of PDA by ~ 50%, **but did not reduce** the incidence of BPD.
- ★ Infants with a PDA (that did not close) had a higher risk of BPD (**55% v. 38%**)
- ★ Infants whose PDA closed spontaneously had a lower incidence of BPD (**30%**) than infants whose PDA closed with indomethacin (**43%**)

* Schmidt B, J Pediatr. 148: 730, 2006

Chronic lung Disease & PDA

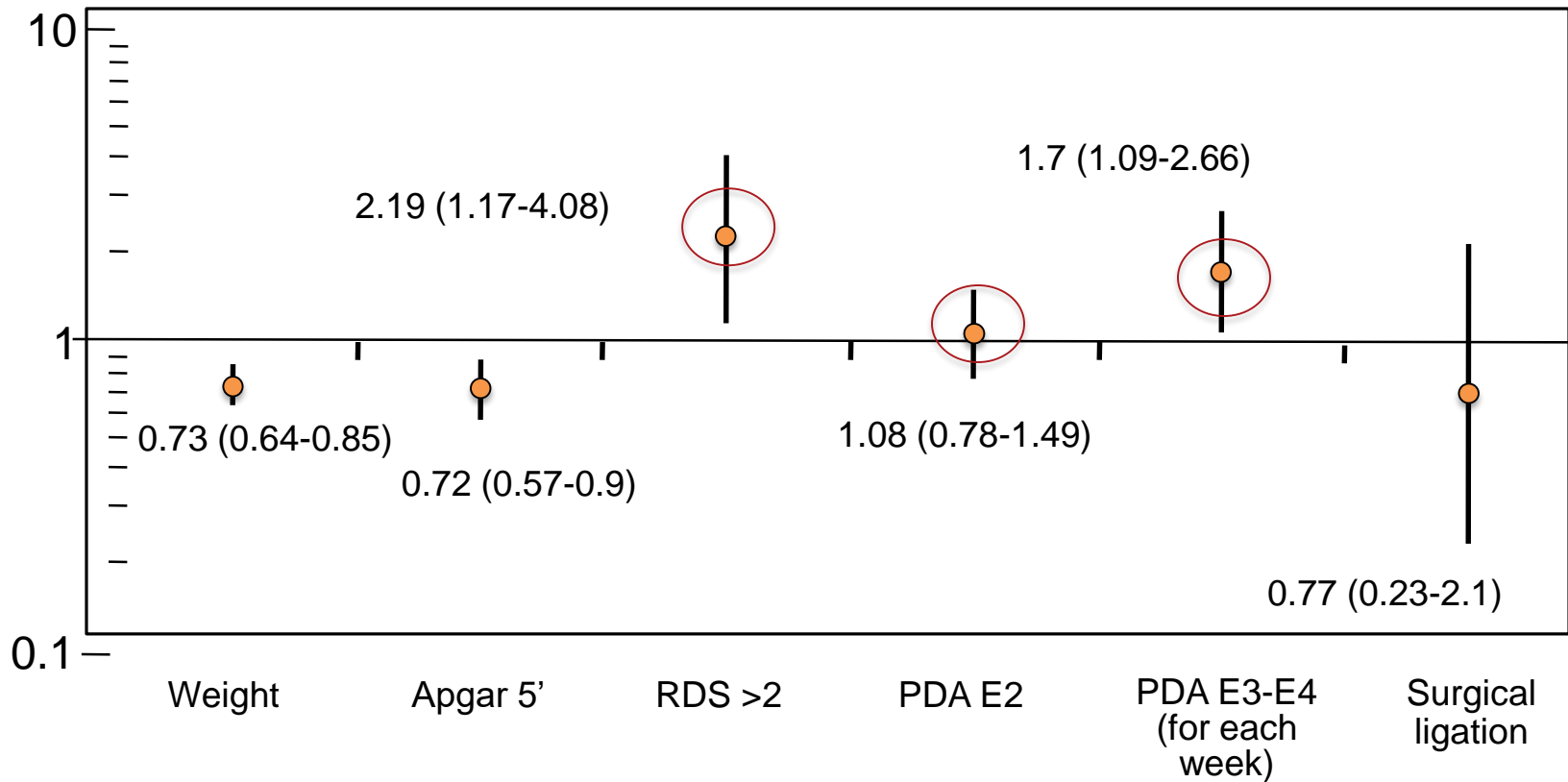
- * Why did the TIPP trial fail to show a benefit?
- * Indomethacin had independent adverse effects
- * The severity of the PDA was not assessed

Does the Duration of Patency and Magnitude of the Shunt Determine the Risk of BPD?

- * Observational retrospective study; Every infant underwent an echocardiographic exam in the first 24 hours and then every 2 weeks until 36 weeks PCA.
- * A PDA staging system* was used to evaluate severity. The system classifies PDA as **E1** (no flow), **E2** (small and non-significant DA), **E3** (moderate HSDA defined using the Echo) and **E4** large HSDA (defined with the ECHO)

Schena et al J Pediatrics
2015

Odds Ratios for BPD or Death

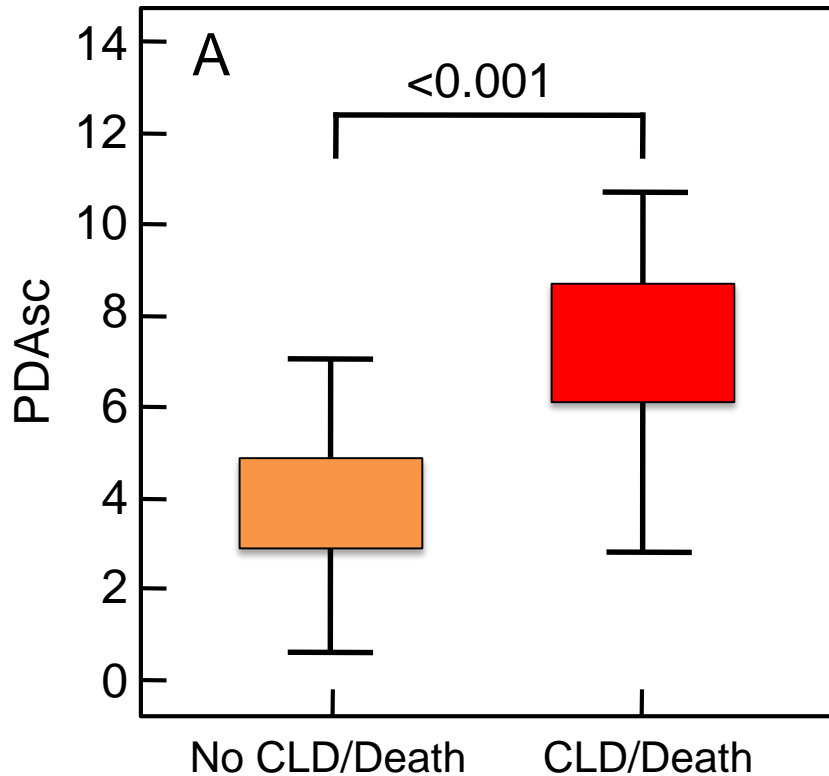


Multivariate analysis, OR for the BPD, or death group controlled for Apgar score at 5 minutes and severity of RDS.

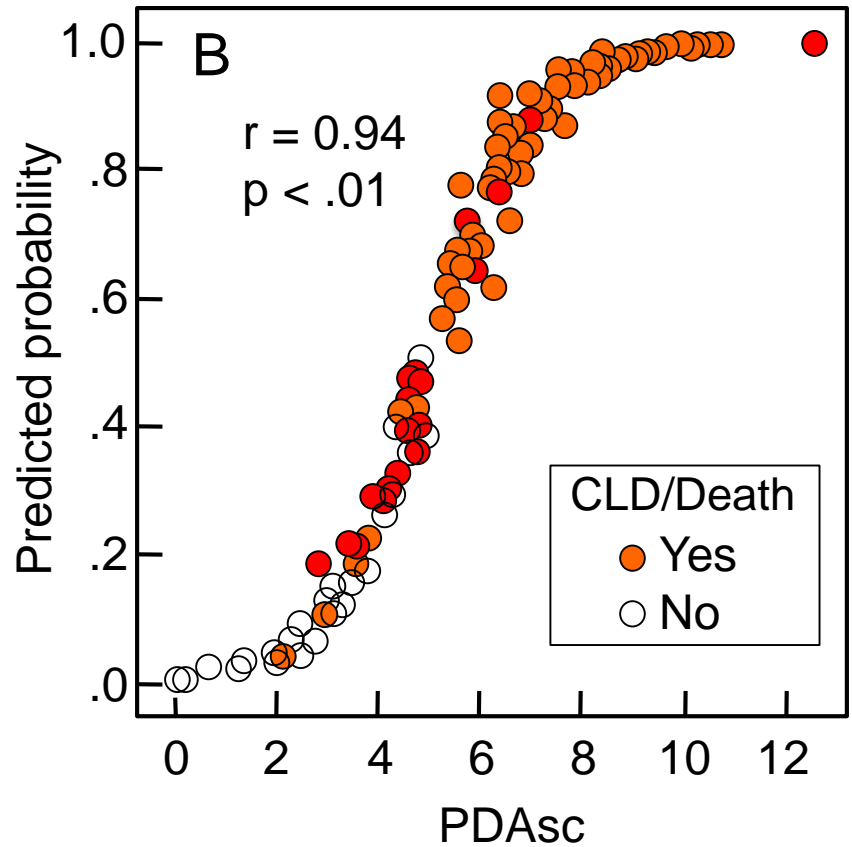
Patent Ductus Arteriosus Severity Score and Risk of Chronic Lung Disease or Death

- ★ 141 infants 26-27 weeks gestation had an echocardiogram at ~ 10 hours, , day 1, day 2 & day 5-7.
- ★ Primary outcome a composite of chronic lung disease or death.
- ★ A **severity score** was determined on the day 2 and ranged between 0 (no PDA) & 13.

PDA severity score in infants with or without CLD or death



Relationship between the severity score & CLD or death



Prophylactic Indomethacin & Chronic Lung Disease The Controversy Continues

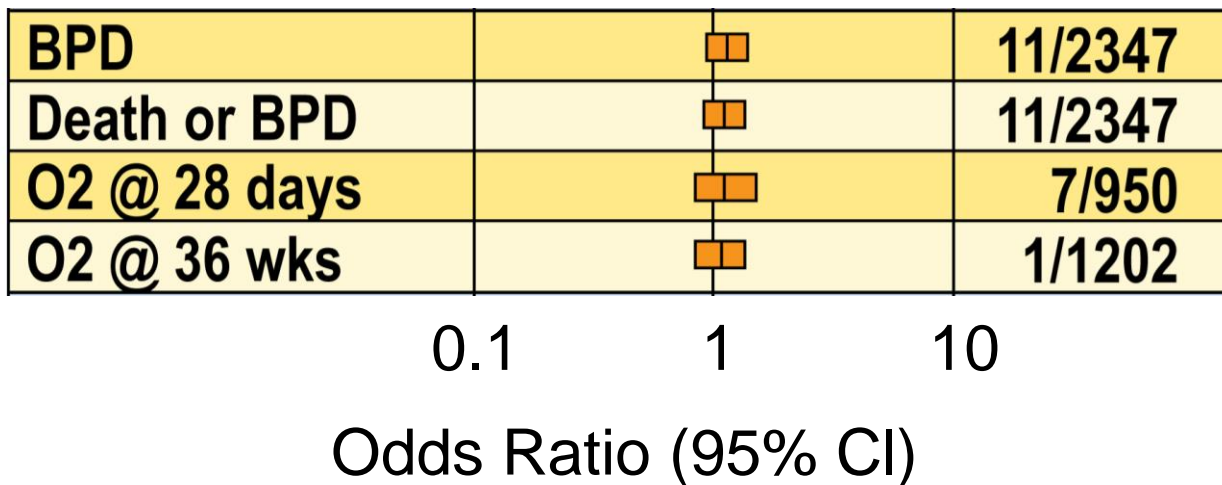
- ★ Prospective double cohort controlled study* of infants < 28 weeks' gestation (n=397). 2005-2011 prophylactic indomethacin; 2011-2016 no infant was treated with indomethacin until day 8 if they had a *moderate to large PDA* .
- ★ Infants treated with prophylactic indomethacin had a lower incidence of *BPD RR 0.68 (0.46-0.89)* and *death/BPD RR 0.78 (0.62-0.95)*
- ★ However, the lack of a relationship between the duration of ductal patency and BPD suggests that it is an association and not causal.

*Liebowitz and Clyman J Pediatr. 2017

Prophylactic Indomethacin & Chronic Lung Disease The Controversy Continues

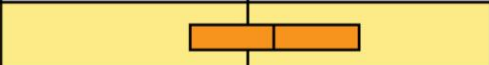
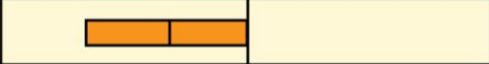
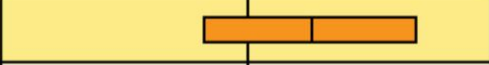
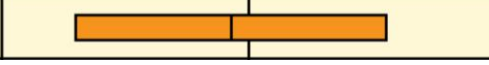
- ★ Retrospective of infant cohort study* < 29 weeks' gestation from the NICHD Neonatal Network comparing infants treated with prophylactic indomethacin in the first 24 hours of life (n=2587) or not (n=5244).
- ★ Prophylactic indomethacin *did not decrease* the risk of BPD or death/BPD.
- ★ However, infants treated prophylactically were smaller, required more resuscitation at birth and needed greater ventilator support.
- ★ Was prophylactic indomethacin ineffective or did it improve outcomes in a sicker population of babies?

Randomized Trials of Indomethacin Prophylaxis for Prevention of Bronchopulmonary Dysplasia



*Does treatment of a PDA before CHF develops
lessen pulmonary morbidity (BPD)?*

Delayed treatment of PDA (3rd or 4th postnatal day) and Bronchopulmonary Dysplasia

BPD		3/180
Death or BPD		2/162
O2 @ 28 days		1/130
O2 @ 36 wks		1/98

0.1 1 10

Odds Ratio (95% CI)

Chronic lung Disease & PDA

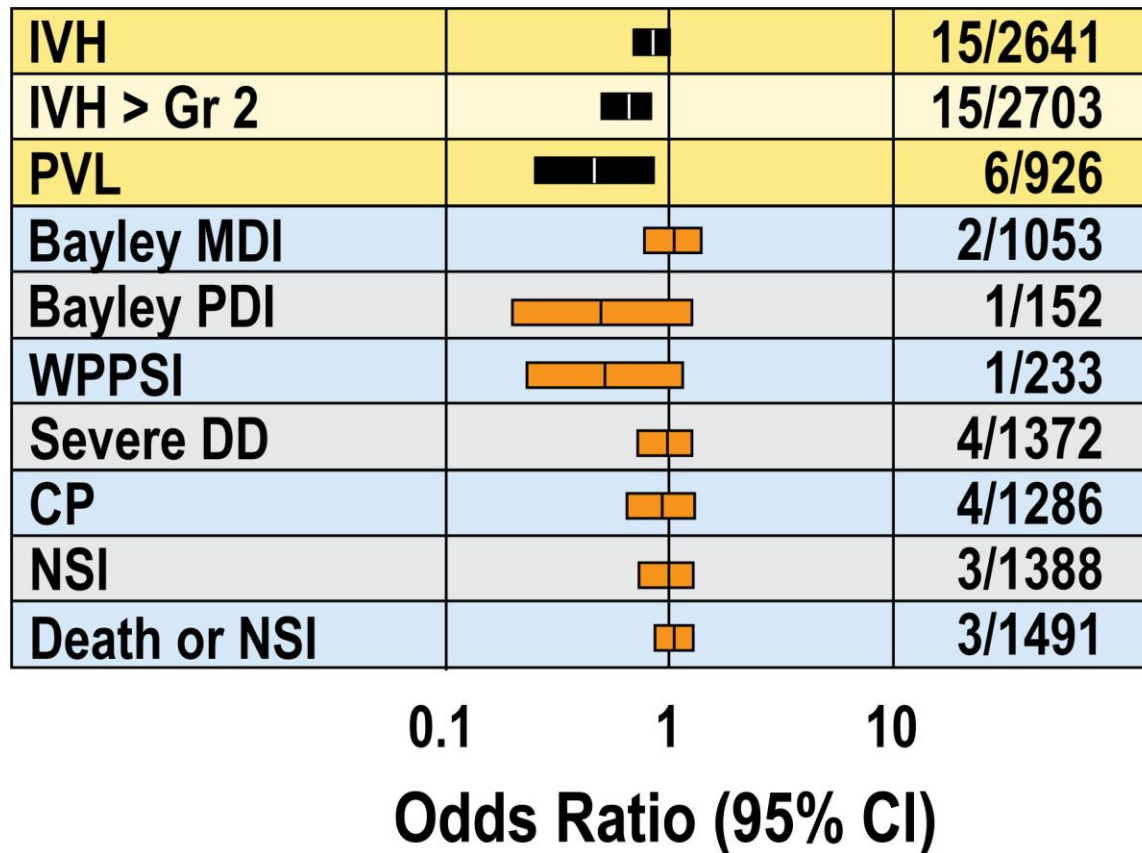
- * Prophylactic indomethacin offers no pulmonary advantages*.
- * Treatment of asymptomatic PDA: no benefit on incidence of BPD*

* Fowle PW and Davis PG Cochrane Database

Intraventricular Hemorrhage & PDA

- ★ Low cardiac output in VLBW infants is associated with an increased risk of IVH
- ★ Cardiac output and blood pressure may be compromised by the presence of PDA.

Randomized trials of Indomethacin Prophylaxis for Prevention of Central Nervous System Injury



Necrotizing Enterocolitis & PDA: A Plausible Hypothesis

- ★ A large left to right shunt through a PDA decreases mesenteric blood flow
- ★ Reversal of blood flow in the descending aorta in infants with a large PDA is an indicator of reduced perfusion to the lower body

Necrotizing Enterocolitis & PDA

- ★ Epidemiological studies do not support an association between PDA & NEC; however it remains controversial.
- ★ Prophylactic indomethacin has not been shown to decrease the incidence of NEC.
- ★ Administration indomethacin to newborn infants may be a cause of focal intestinal perforation (especially when given with postnatal steroids)

Which Infants Would You Treat?

- ★ A 24 weeks gestational age infant at 12 hours of life on mechanical ventilation with a *large* PDA.
- ★ A 26 weeks gestational age infant at 14 days of life with a *large* PDA on CPAP/21% oxygen
- ★ A 28 weeks gestational age infant at 7 days of life with a *large* PDA on CPAP/35% oxygen and increasing oxygen requirements.

Indomethacin and Ibuprofen

- ★ COX-1 & COX-2 are expressed in the ductus arteriosus
- ★ Both isoforms of cyclooxygenase are inhibited by indomethacin and ibuprofen.
- ★ Indomethacin is more potent against COX-1, but also affects COX-2: Ibuprofen also affects COX-1 & COX-2, but is less COX-1 selective than indomethacin

Ibuprofen v. Indomethacin for Treatment of Patent Ductus Arteriosus

- * Cochrane analysis: (21 studies n = 1102) Both drugs are equally effective for closing a PDA
- * Ibuprofen caused less of an increase in serum creatinine and the incidence of decreased urine output (< 1cc/kg/hr) was less than indomethacin.
- * Risk of NEC is less with ibuprofen than indomethacin (0.64 (CI 0.45-0.93) [Ohlsson A et al Cochrane Database Issue 4 2015](#))

Only Indomethacin has been Shown to Prevent IVH

- * Indomethacin alters basement membrane components in cerebral vessels leading to increased stability of the vessel.
- * Indomethacin (but not ibuprofen) may decrease the risk of a reperfusion injury, by limiting CBF.

*Things to consider when choosing indomethacin or
ibuprofen **beyond the first 24 hr after birth:***

Morbidity

*Ibuprofen better than
indomethacin?*

Success of PDA closure (28 wks)

Similar

Oliguria

Better

Elevated creatinine

Better

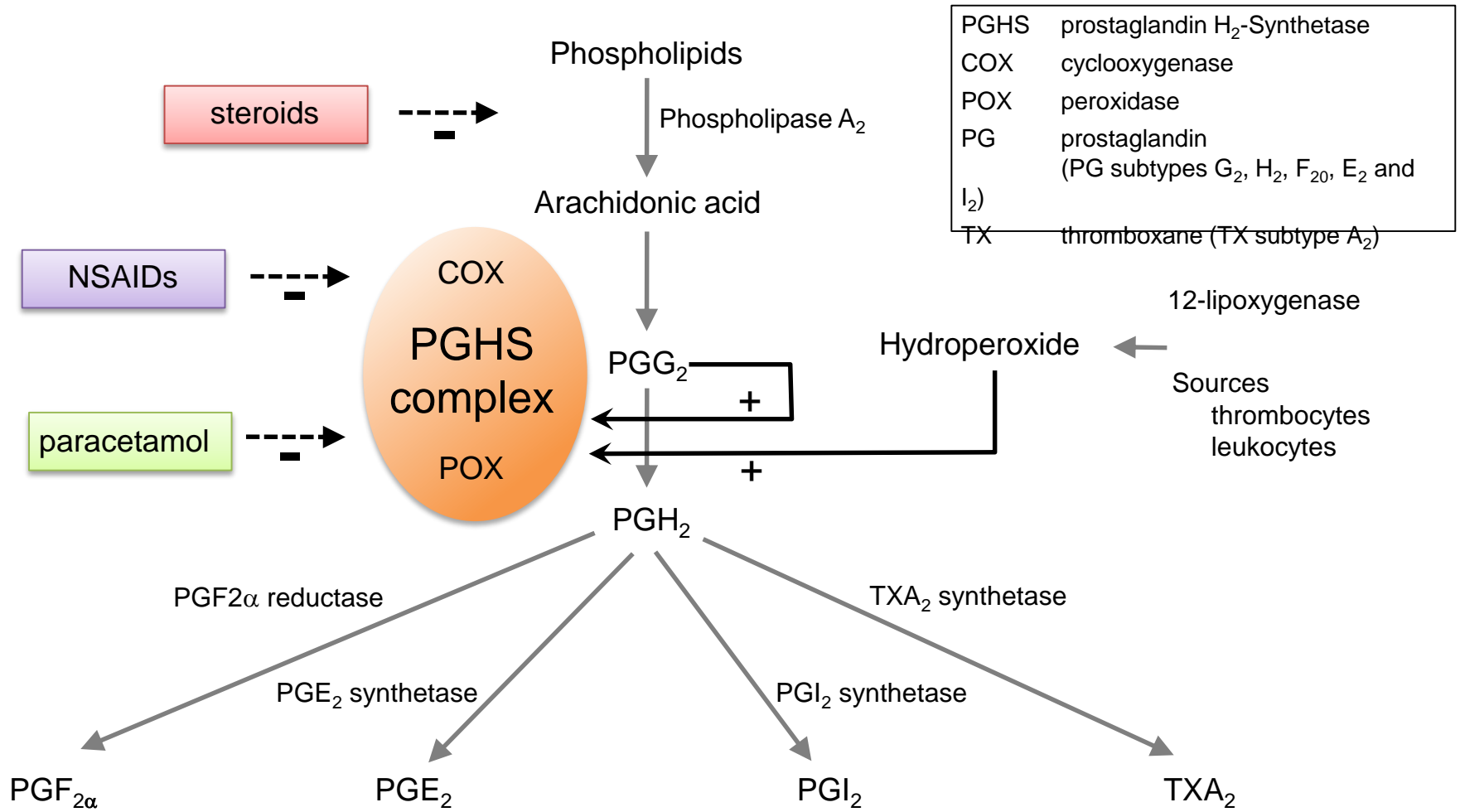
Bilirubin toxicity risk

Theoretical

NEC

Better

Paracetamol

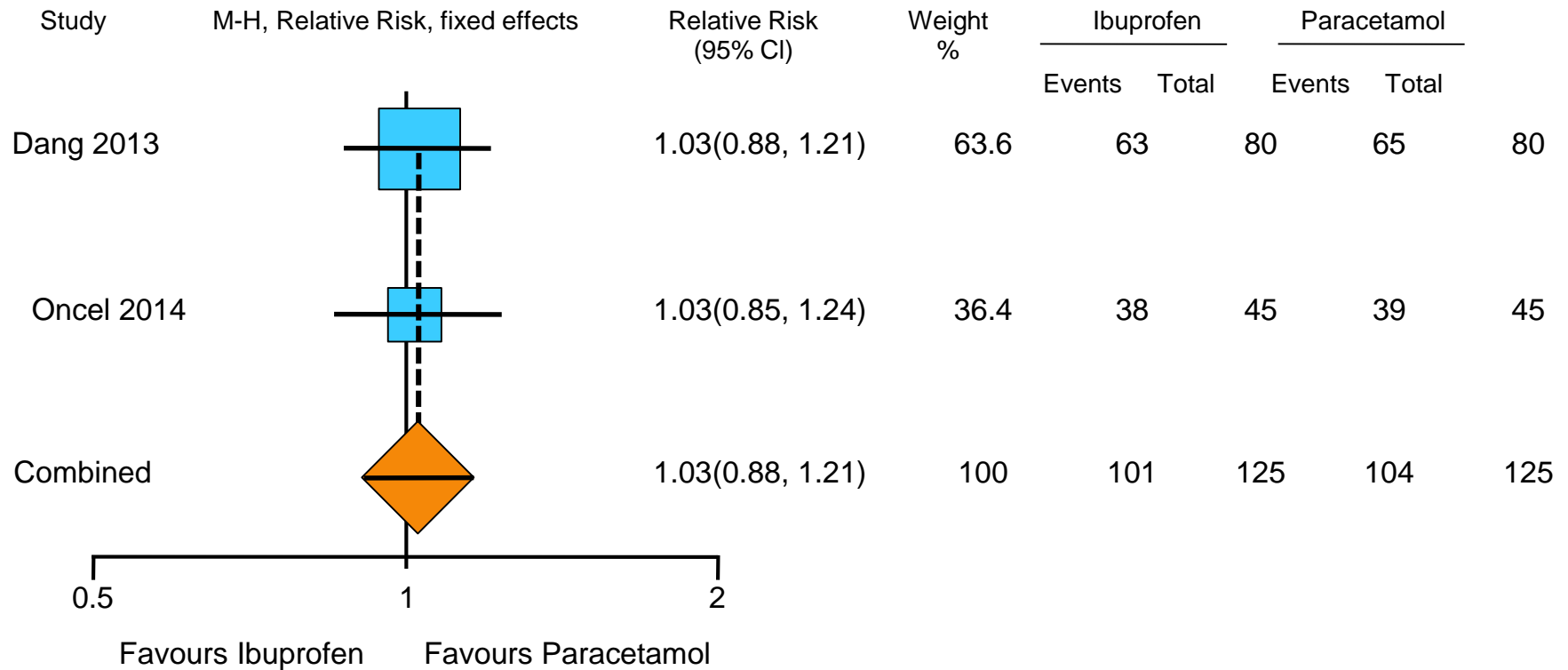


Paracetamol for PDA

- ★ Recent RCTs suggests equivalency of oral paracetamol with oral ibuprofen*. (n=90 and n = 160)
- ★ Animal data suggests less potency than indomethacin@
- ★ The dose of paracetamol recommended for closure of the ductus is much higher than for febrile infants (60 mg/kg/day).
- ★ There is a paucity of safety (hepatic toxicity) and efficacy data.

* Oncel et al J Pediatr. 2014. & Dang et al PLOS one 2013
@ Khuffash et al Pediatric Research 2014

Ductal closure after ibuprofen or paracetamol treatment in randomised controlled trials after 6 days from starting treatment



Are Feedings Safe in Infants Receiving NSAIDs?

- * 177 infants (23 1/7 – 30 6/7) weeks were randomized to trophic feedings (15 ml/kg/day) or no feeding, while receiving NSAIDs.
- * 40 infants received ibuprofen and 137 received indomethacin.
- * Standardized feeding protocol was used.
- * Infants randomized to the feeding arm required fewer days to reach 120 ml/kg/day. ($p = 0.001$)
- * No difference in rates of feeding related morbidities (NEC or SIP)

*Clyman et al. J Pediatr. August 2013

Surgical Closure of Patent Ductus Arteriosus is Controversial (Adverse Effects)

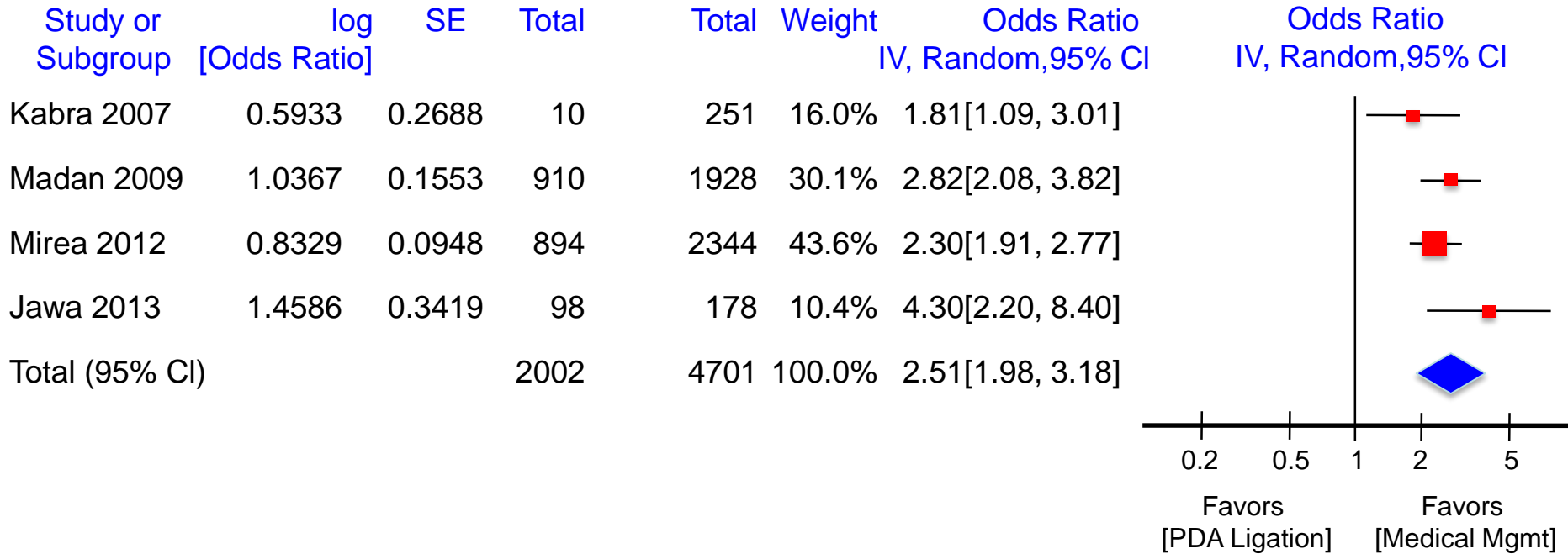
- ★ Surgical ligation is associated with an increased incidence of diaphragmatic paresis, paresis of the left vocal cord, late development of scoliosis, neurodevelopmental impairment and chronic lung disease.

*Meta-analysis of PDA Ligation and Health Outcomes
(29 cohort studies and one RCT)*

- ★ This meta-analysis was based on 39 cohort studies and only one RCT.
- ★ All the cohort studies had a moderate risk of bias due to a failure to adjust for *survival bias* and important *pre-ligation confounders* (e.g., ventilator dependence, IVH etc.)

Meta-analysis of PDA Ligation and Health Outcomes

Chronic lung disease: aOR 2.51 (CI 1.98-3.18)



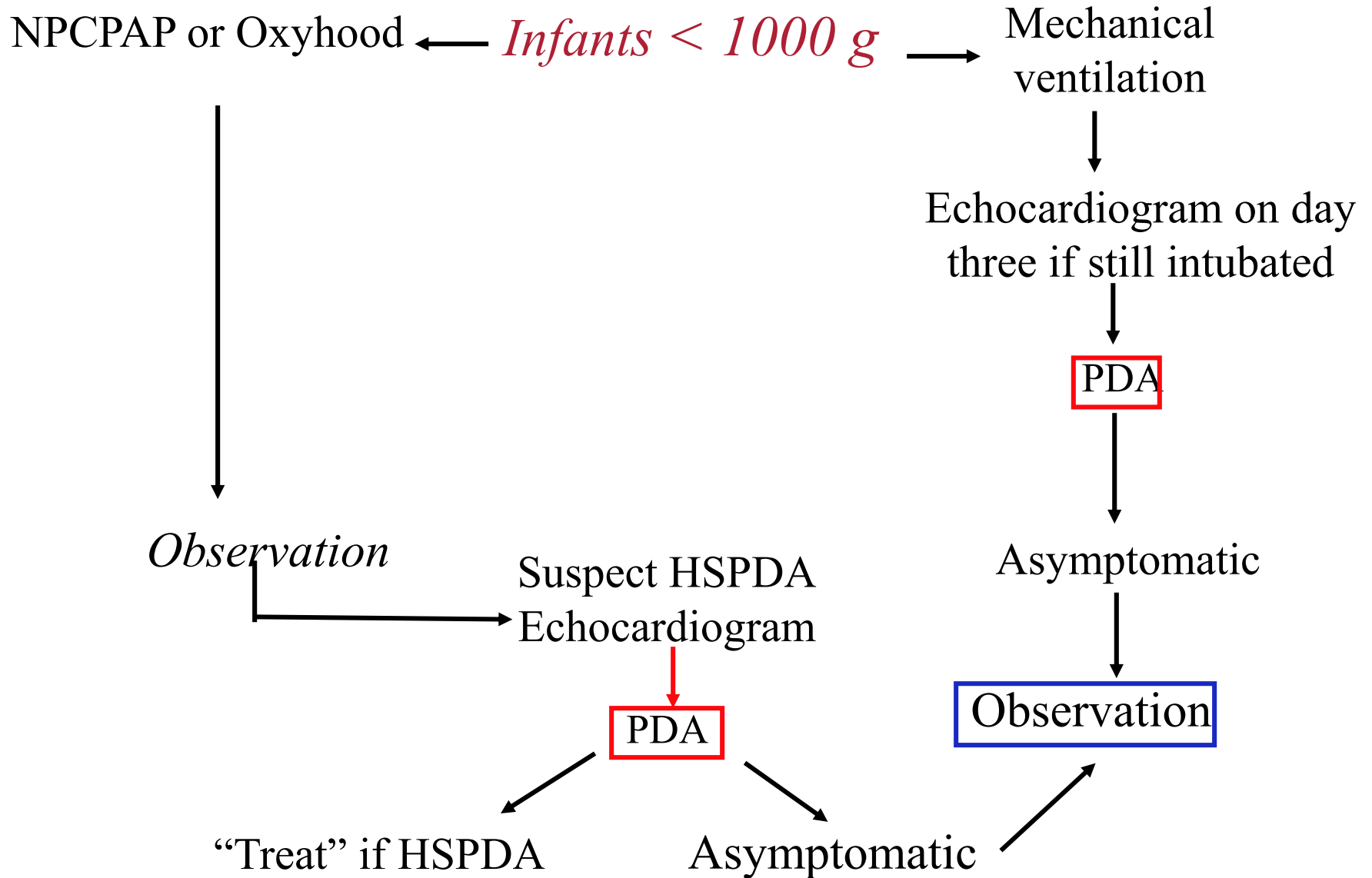
Association of PDA Ligation with Death or NDI in ELBW Infants

- ★ Retrospective, observational study of 754 infants with a hemodynamically significant PDA; 24% underwent surgical ligation and the rest were treated medically.
- ★ Infants who were treated with ligation had a higher frequency of morbidities “pre-ligation”(NEC, sepsis, dependence on mechanical ventilation)
- ★ *After controlling for perinatal characteristics and pre-ligation morbidities, there were no significant differences in death/NDI, chronic lung disease or ROP.*

Neurodevelopmental Outcomes of Premature infants treated for PDA

- * Follow-up study (retrospective/observational) at age 2-3 years of 1473 infants (< 29 weeks gestation); 826 infants required no treatment, 569 required medical treatment and 78 needed surgical ligation
- * *Infants treated medically (aOR 1.622 (CI 1.199-2.196) or surgically (aOR 2.001 (CI 1.126-3.556) had an increased risk of adverse neurodevelopmental outcomes.*

Management of PDA



Criteria for a Hemodynamically Significant PDA

- ★ Signs of CHF (or reduced cardiac output)
- ★ Failure to wean ventilator settings or an increased need for ventilator support **with no other cause**.
- ★ Echocardiographic criteria: Ductal size (> 3mm), PDA/LPA ratio, LA/Ao ratio, LVO/SVC ratio, LPA diastolic velocity, increased LV end diastolic diameter.
- ★ Biochemical markers: β natriuretic peptide, troponin-T & N-terminal-pro hormone atrial natriuretic peptide

Hemodynamically Significant PDA

*Indomethacin or
Ibuprofen*

Ductus closed by
echocardiogram

PDA+Asymptomatic

PDA+Symptomatic

Observation

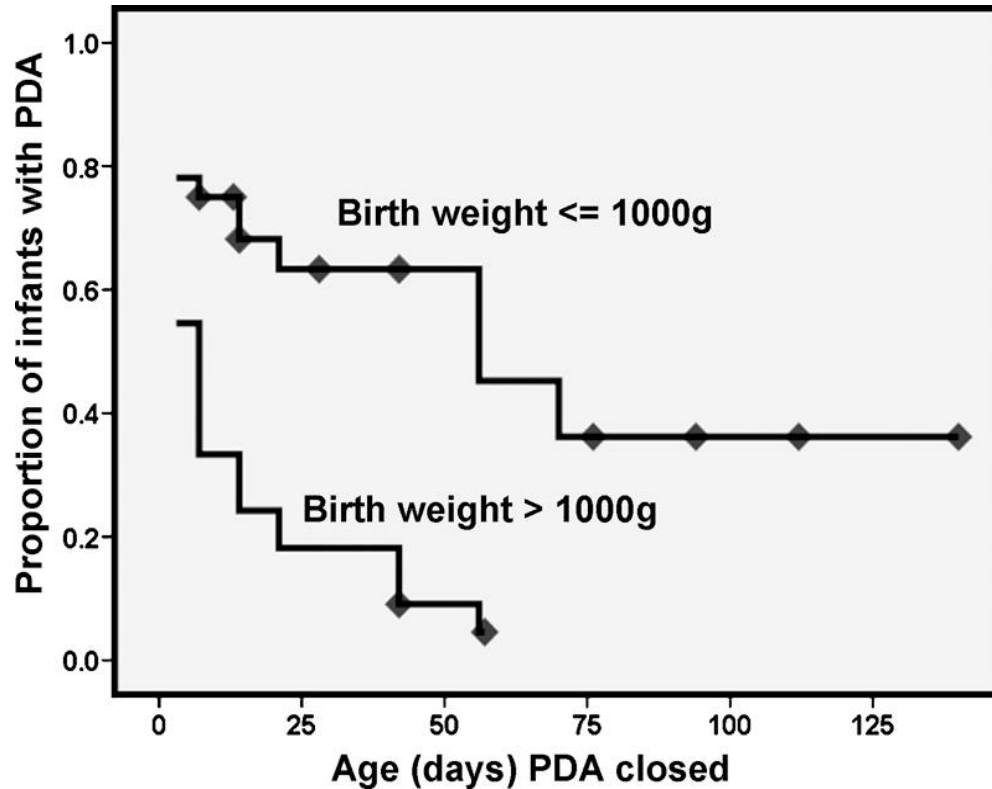
Repeat indomethacin or ibuprofen
(adjust dose for postnatal age)

Consider surgical ligation if
persistently symptomatic

Does a Conservative Approach Increase Morbidity?

- ★ Double-blind RCT in infants 23-32 weeks gestation
- ★ Infants randomized to **early treatment** (3 days) with ibuprofen (n=54) or **expectant management** who were treated only if the PDA were hemodynamically (HS) significant (n = 51).
- ★ In the expectant group only 20% developed a HS PDA.
- ★ 49% of the expectant group never received ibuprofen or ligation.
- ★ No difference in the incidence of morbidities including BPD, ROP, IVH, PVL and NEC.

What is the Natural History of PDA in the VLBW Infant?

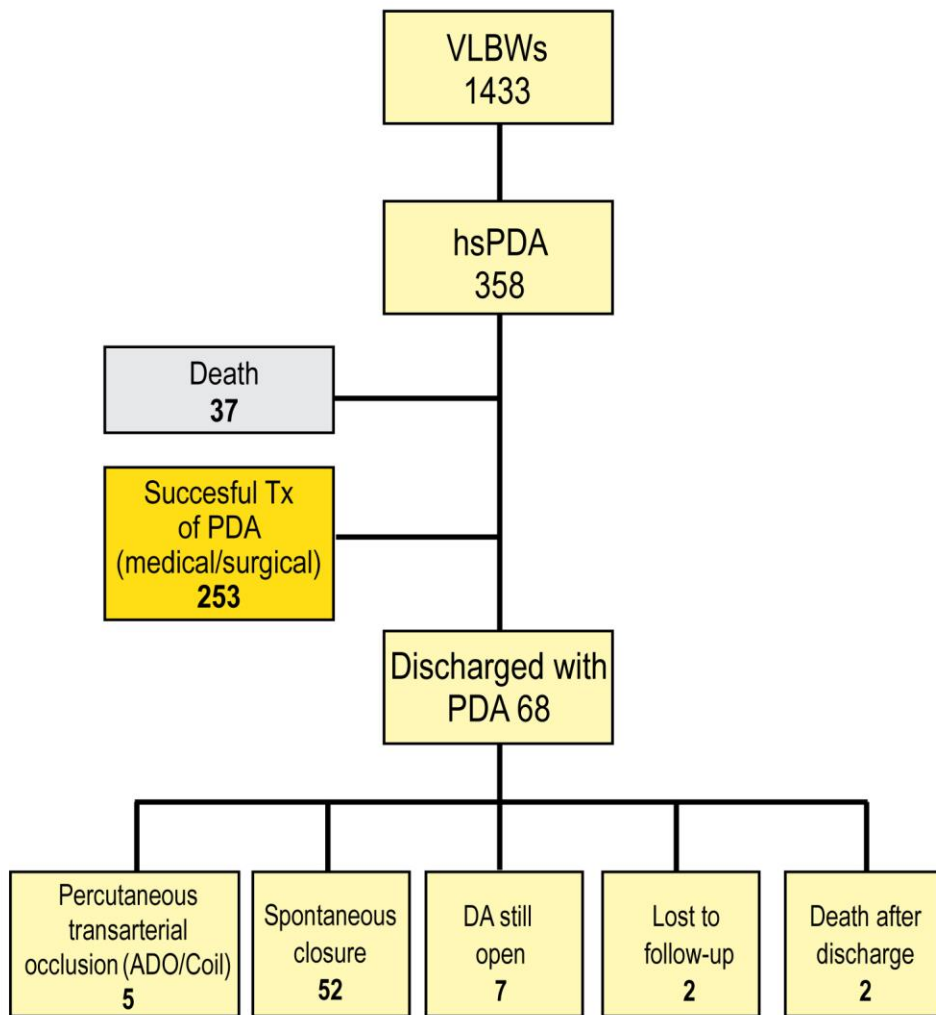
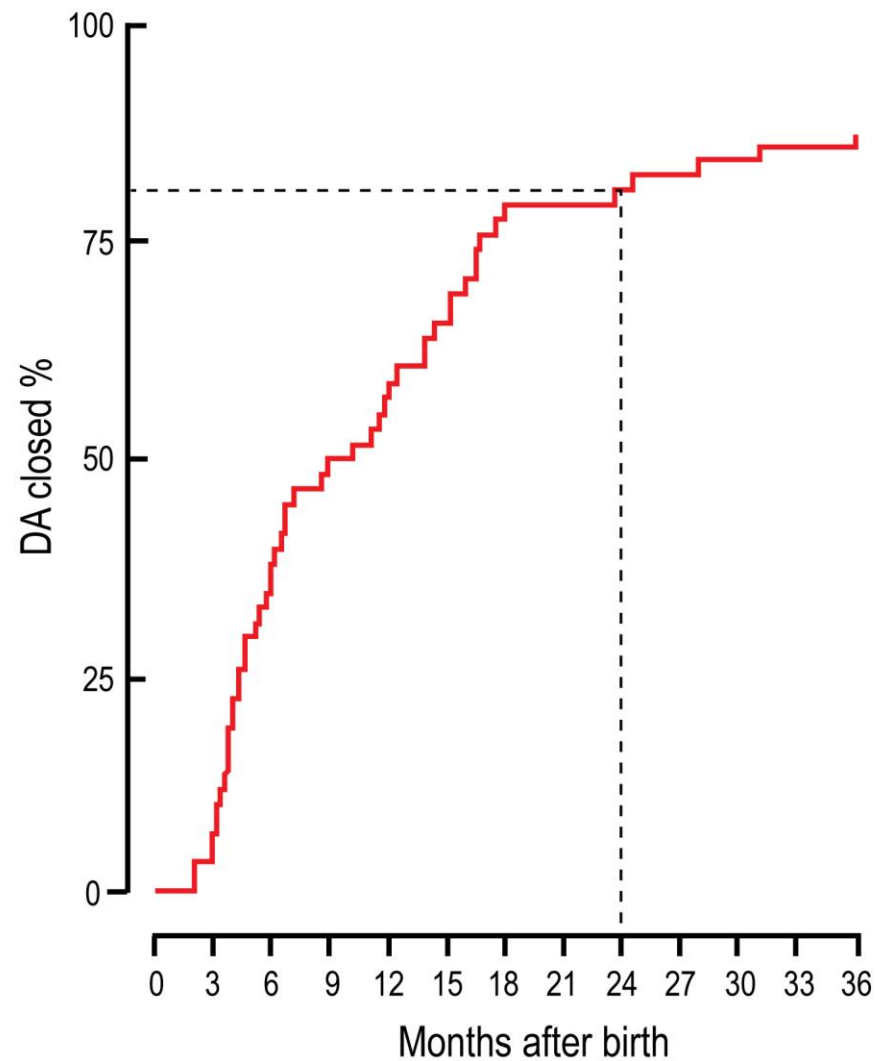


- ▣ The DA closed spontaneously in 49% of infants by day 7.
- ▣ 97% of infants > 1000 g did not require intervention and 2/3 closed by 7 days (vs. 31% of infants < 1000g)

What is the Natural History of PDA in the ELBW Infant?

- * Retrospective cohort study of 1433 VLBW infants of which 68 were discharged with a PDA.
- * 68 infants were discharged and data on 64 analyzed.
- * **52 of the 64 infants had spontaneous closure**; The median time of closure was 9 months (49 weeks PMA).
- * The majority of PDAs closed within the first 24 months.

Weber S. J Pediatrics 2015

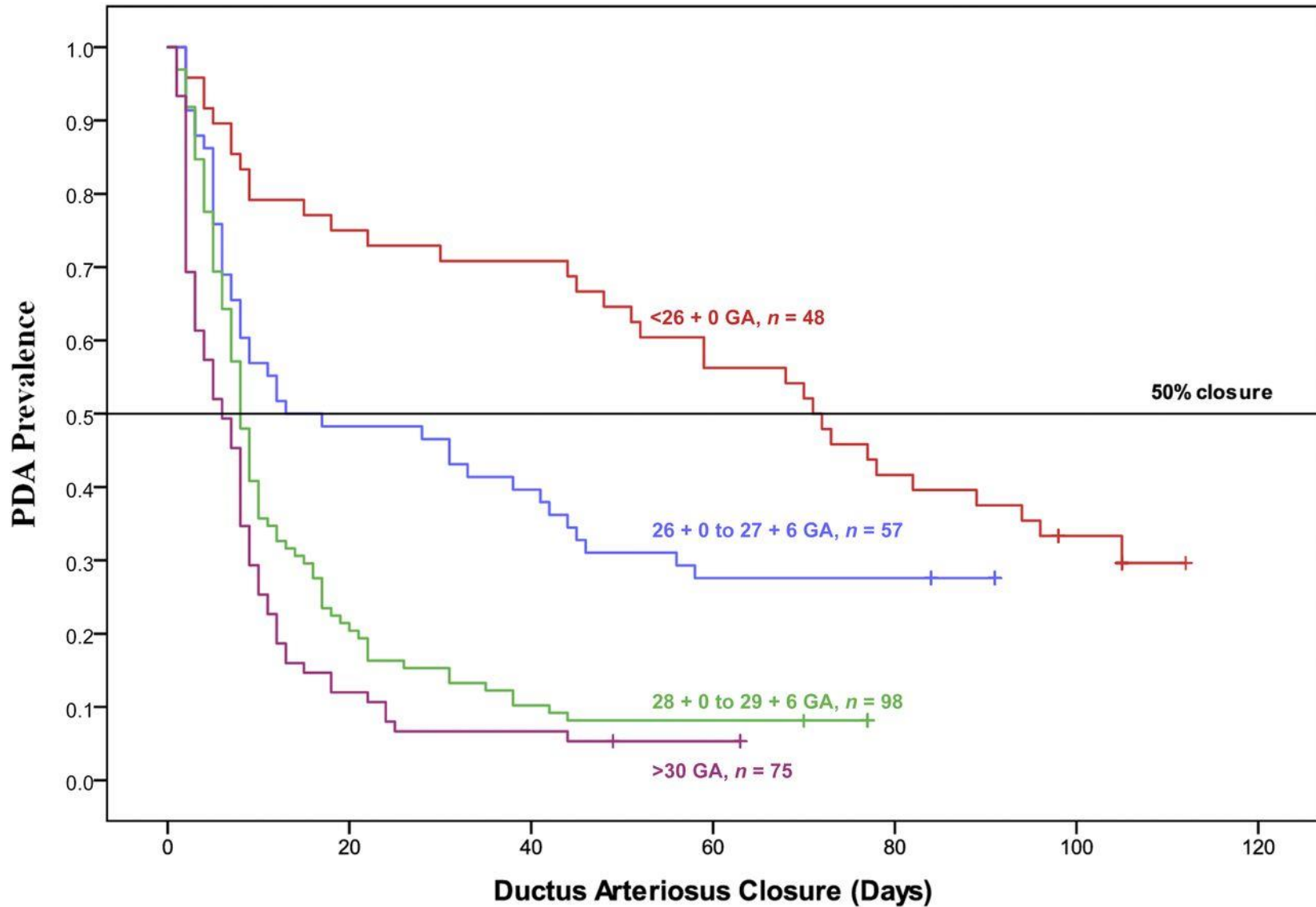
A**B**

Natural History of the Ductus Arteriosus Closure

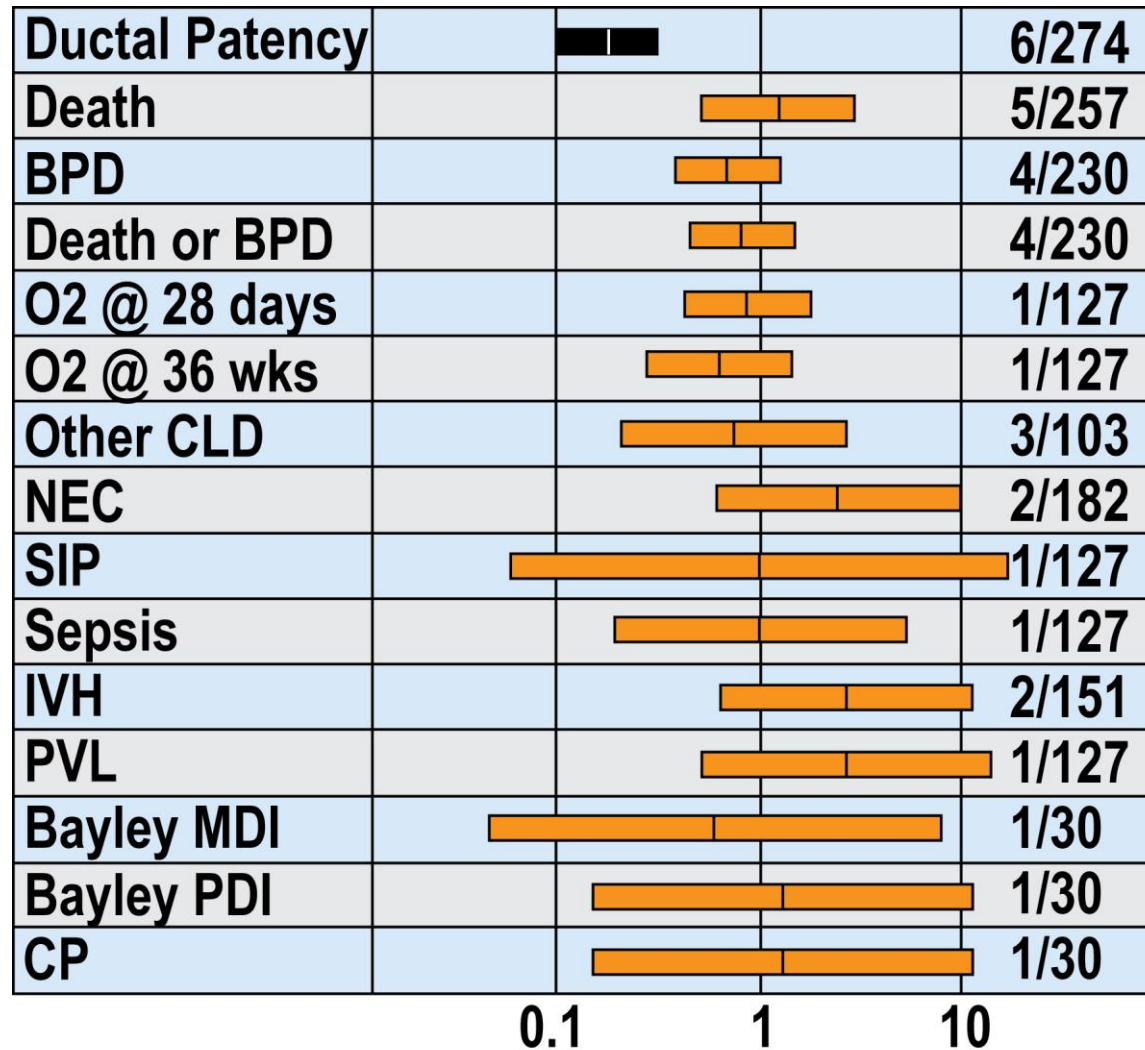
- * N = 280 VLBW infants managed conservatively and surviving until discharge (mean BW 1112 grams; mean GA 29 weeks)
- * A targeted ECHO was performed in the first week of life and then at 1-2 week intervals until ductal closure.
- * 85% closed before hospital discharge and 56% of infants with a patent ductus at discharge closed (24/43)

Semberova et al Pediatrics 2017

Closure of the Ductus Arteriosus Before Discharge



Treatment of the Symptomatic PDA



Odds Ratio (95% CI)

Patent ductus arteriosus: to treat or not to treat?

- ★ There have been 53 randomized controlled trials of PDA closure in preterm infants (>5,000 subjects)
- ★ Neither individual trials nor meta-analyses have demonstrated long term benefits of measures to close the ductus arteriosus (medically or surgically) in the first two weeks of life (level of evidence 1A).
- ★ Benefits are limited to **fewer ductal ligations and decreased IVH (> grade & PVL (with prophylactic indomethacin))** with no improvement in neurodevelopmental outcomes.

Conclusions & Recommendations

- ★ There are no convincing data that ligation of an asymptomatic PDA is beneficial.
- ★ Fluid restriction may help reduce the incidence of PDA and should be considered part of first line therapy in symptomatic infants*.

* In an observational study (n= 18) fluid restriction offered no benefit on pulmonary or systemic hemodynamics (*Buyst JD et al J Pediatr. 2012;161: 404-8*)

Conclusions & Recommendations

- ★ Ductal ligation is rarely required in preterm infants who are not ventilated (e.g., NPCPAP)
- ★ Indomethacin or ibuprofen should be reserved for the ventilated, symptomatic infants (cardiopulmonary compromise) with a PDA; however empiric data to inform decisions are lacking.
- ★ Surgical ligation should be avoided if possible.