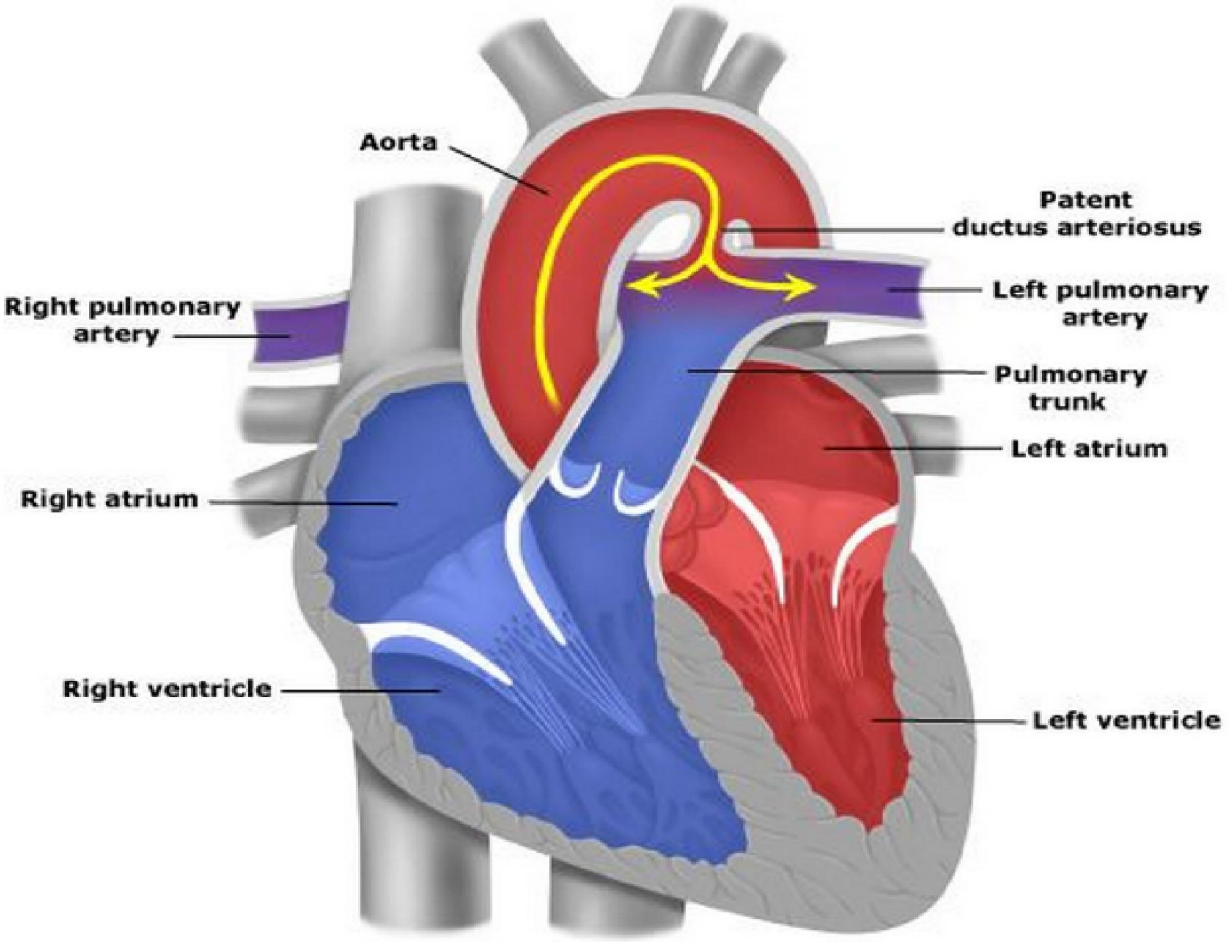
PARACETAMOL FOR PATENT DUCTUS ARTERIOSUS CLOSURE IN PRETERM INFANTS (REVIEW)

Emergency Department

Children's Hospital 2

Patent ductus arteriosus



OVERVIEW

- Preterm infants with moderate to large left-to-right shunts:
  - Greater mortality rate
  - Increased risk of pulmonary edema, hemorrhage and bronchopulmonary dysplasia
  - Decrease in perfusion and oxygen delivery to end-organs

MANAGEMENT OF PDA

- Supportive care
  - Fluid restriction 110 – 130 mL/kg
  - Permissive hypercapnia, low PaO_2 targets, PEEP
  - Chlorothiazide is considered
  - Hct 35 - 40%
  - Neutral thermal environment
- Cyclooxygenase inhibitors: indomethacin & ibuprofen (Grade 2B)
- Surgical ligation

UpToDate

CONTRAINDICATIONS OF INDOMETHACIN

- Proven or suspected infection untreated
- Active bleeding
- Thrombocytopenia, coagulation defects
- Necrotizing enterocolitis
- Significant impairment of renal function
- Congenital heart disease in which patency of the ductus arteriosus is necessary

IBUPROFEN

- Good points
  - As effective as indomethacin in closing PDA
  - Associated with a lower risk of NEC, transient renal insufficiency
  - Economic preference
- Not-good points
  - Contraindications for ibuprofen are similar to those for indomethacin (except for NEC & RF)
  - Average peak bilirubin levels were higher

PARACETAMOL

- PARACETAMOL
  - A analgesic, antipyretic drug, weak anti-inflammatory
  - Used in all age groups
  - In high concentrations inhibits the synthesis of prostaglandins

Paracetamol vesus Ibuprofen for patent ductus arterious closure in preterm infants?

PARACETAMOL
FOR PATENT DUCTUS ARTERIOSUS
IN PRETERM INFANTS

THE COCHRANE
COLLABORATION®

METHODS

- **Size**
  - 2 RCTs: Dang 2013, Oncel 2013
  - n = 250
  - Three others is ongoing
- **Types of participants**
  - Infants born preterm (< 37 weeks PMA) or with low birth weight (< 2500 g)
  - Echocardiographic diagnosis of a PDA

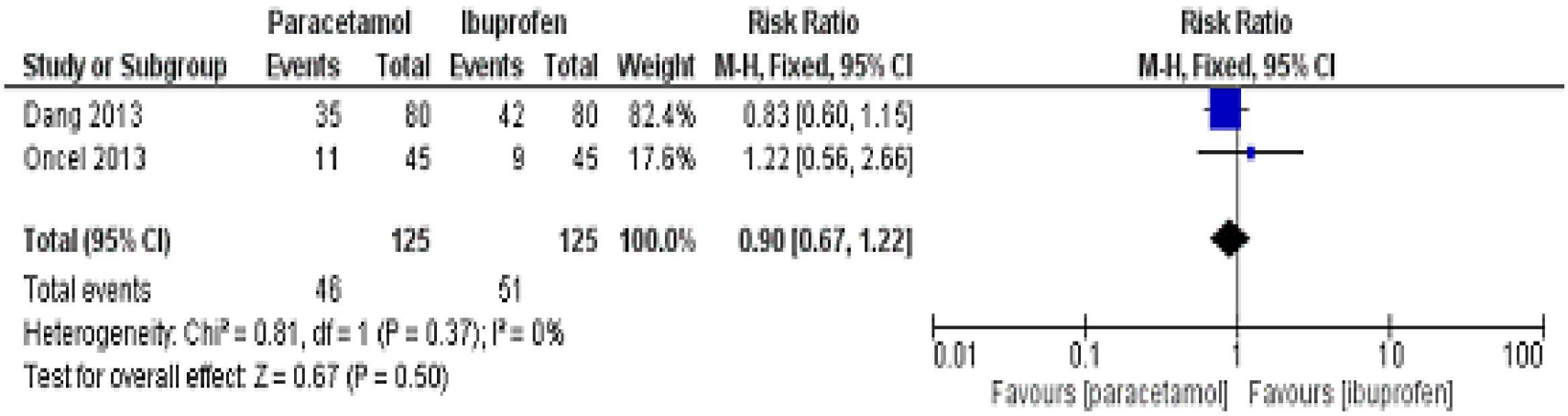
METHODS

- **Types of interventions**
  - The paracetamol group: 15 mg/kg orally every 6 hours for 3 days
  - The ibuprofen group: initial dose of 10 mg/kg orally followed by 5 mg/kg after 24 and 48 hours

PRIMARY OUTCOME

- Failure of PDA closure after the first course of paracetamol treatment

Figure 3. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.1 Failure of ductal closure after the first course of treatment.



PRIMARY OUTCOME

- Both studies (n = 250 infants) reported on this outcome
- There was no significant difference between the paracetamol and the ibuprofen groups in failure of PDA closure (typical RR 0.90, 95% CI 0.67 to 1.22; typical RD -0.04, 95% CI -0.16 to 0.08; I2 = 0% for RR and I2 = 23% for RD)

SECONDARY OUTCOMES

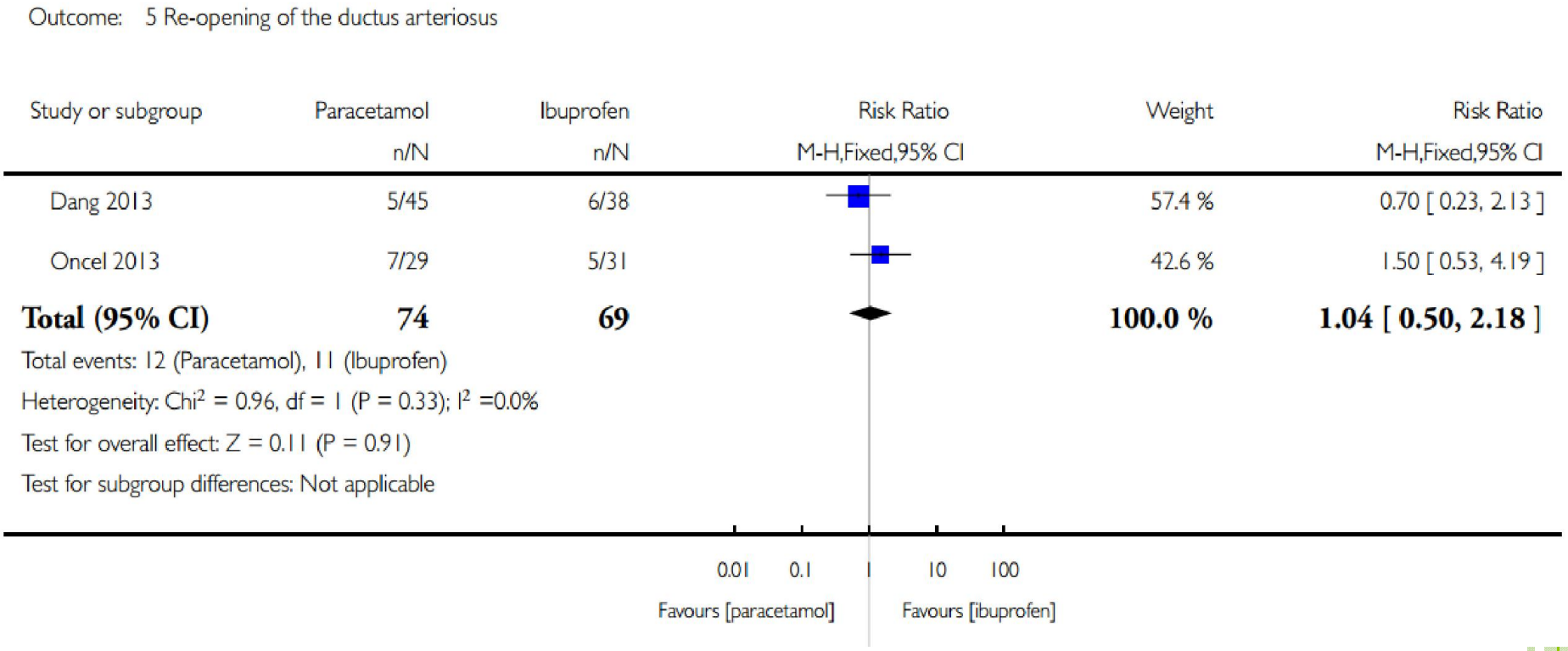
- There was no significant difference between the paracetamol and the ibuprofen groups in
  - All-cause mortality during initial hospital stay
  - Neonatal mortality (death during the first 28 days of life)
  - Infant mortality (death during the first year of life)

SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Re-opening of the ductus arteriosus
  - Surgical closure of the PDA following treatment failure

SECONDARY OUTCOMES

- Re-opening of the ductus arteriosus



SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Duration of ventilator support (days)
  - Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death, in days)

SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Pulmonary hypertension
  - Bronchopulmonary dysplasia (BPD) at 28 days & at 36 weeks PMA
  - Moderate to severe BPD according to the new criteria
  - Severe BPD defined according to the new criteria

SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Pulmonary haemorrhage (blood stained liquid flowing from the trachea of the infant)
  - Intraventricular haemorrhage
  - Severe IVH (Grade III-IV)
  - Gastrointestinal bleed

SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Periventricular leukomalacia
  - Necrotizing enterocolitis (NEC) (any stage)
  - Intestinal perforation (do not occur)
  - Retinopathy of prematurity (ROP) any stage
  - ROP stage ≥ 3
  - ROP requiring laser therapy

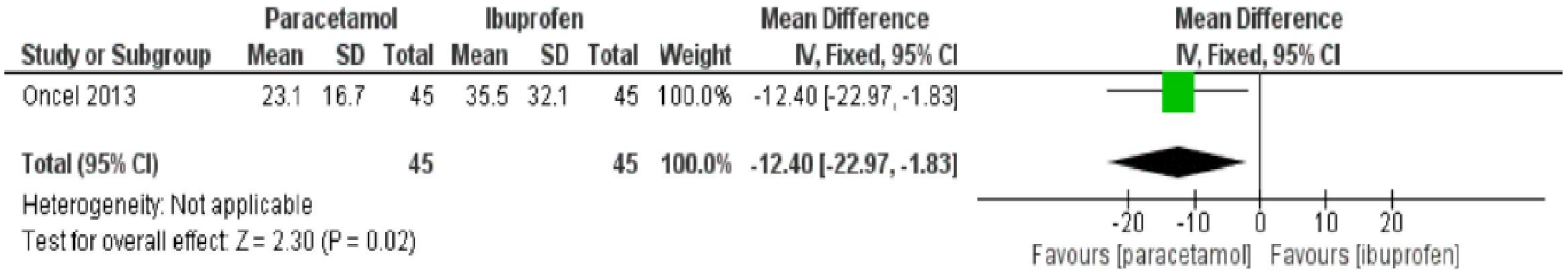
SECONDARY OUTCOMES

- There was no significant difference between the paracetamol and the ibuprofen groups in:
  - Sepsis
  - Oliguria
  - Serum or plasma levels of creatinine, AST/ALT, bilirubin after treatment
  - Liver failure did not occur

SECONDARY OUTCOMES

- Duration of need for supplementary oxygen (days)

Figure 4. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.10 Duration for need of supplementary oxygen (days).



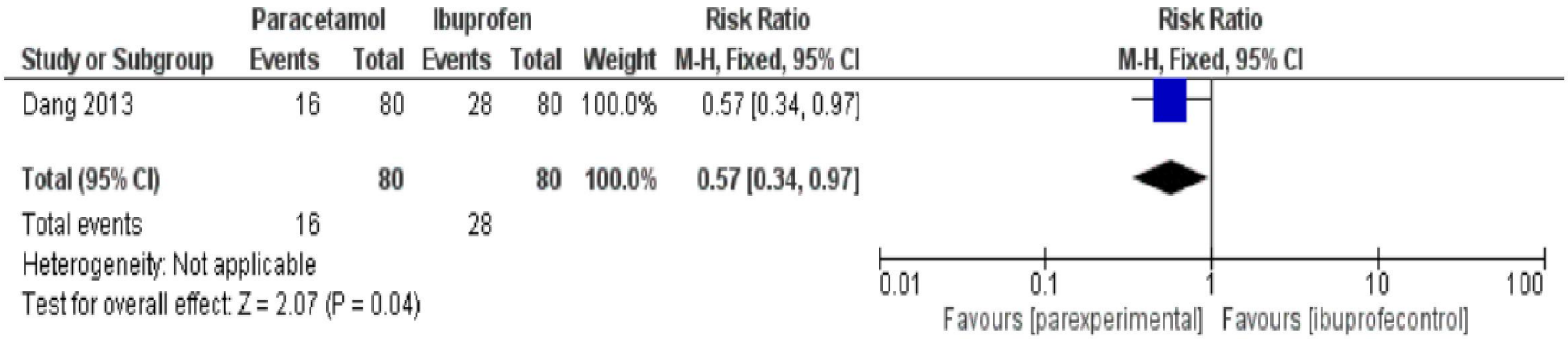
SECONDARY OUTCOMES

- One study (n = 90) reported on this outcome
- There was a significant difference between the paracetamol and the ibuprofen groups in the duration of need of supplementary oxygen, favouring the paracetamol treated group (MD -12.40 days, 95% CI -22.97 to -1.83)

SECONDARY OUTCOMES

- Hyperbilirubinaemia

Figure 5. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.30 Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and body weight.



SECONDARY OUTCOMES

- One study reported on this outcome (n=160)
- There was a significant difference in hyperbilirubinaemia favouring the paracetamol groups (RR 0.57, 95% CI 0.34 to 0.97; RD -0.15, -0.29 to -0.01; NNTB 7, 95% CI 3 to 100)

CONCLUSION

- Oral paracetamol is an potential drug to PDA closure in preterm infants
- Further research regarding the effect and safety of paracetamol in PDA closure is needed before recommendation can be started

THANK YOU
FOR YOUR ATTENTION!